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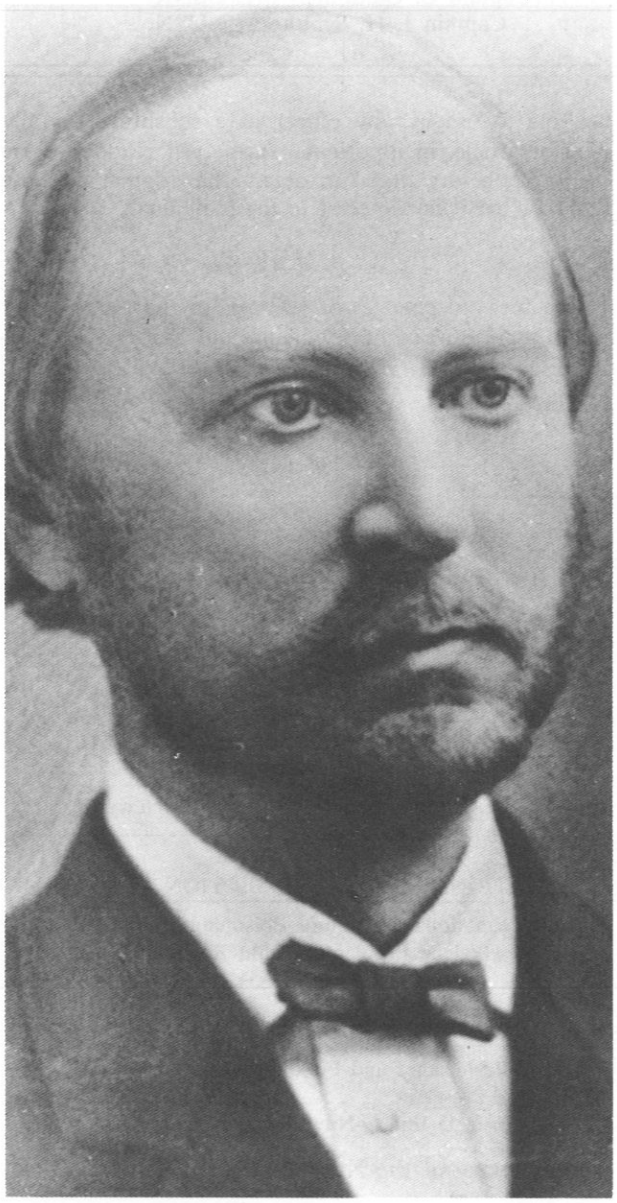

Surgeons General of the Past
(The ninth in a series of brief biographies)

William Grier, the ninth Chief of the Bureau and fifth Surgeon General of the Navy, was born in Ireland on 5 October 1818, and came to this country as a child with his parents. He probably studied medicine under a preceptor and possibly at the University of Maryland, since he was appointed Assistant Surgeon from Maryland at the age of 20 on 7 March 1838, by President Van Buren. His first service was on the sloop Cyane in the Mediterranean Squadron. He was later assigned to the naval hospital at New York and next served with what was then called the North Pacific Squadron. After promotion to Surgeon on 14 April 1852 he became Fleet Surgeon of the North Pacific Surveying Expedition from 1853 to 1856. This expedition supplemented the surveys made by the famous Wilkes Expedition in the Southern Pacific from 1838–1842. During the Civil War, Doctor Grier was first attached to the sloop Macedonian and later between 1863 and 1865 to the hospital Pinckney, the Western Flotilla's temporary naval hospital at Memphis, Tennessee. He afterwards served at the naval hospital in Annapolis and as a member and President of the Board of Medical Examiners at Washington. He was appointed Surgeon General with the relative rank of Commodore by President Grant on 3 February 1877. Doctor Grier was retired on 5 October 1878 but he lived until 11 January 1911. His 40 years in the Navy and 93-year life from the President Monroe to the President Taft administrations, witnessed the coming of railroads, the telegraph, telephone and steamships. He lived through the change from sail to steam, from broadside to turret, and from the old wooden line of battle ship to the steel dreadnaught. In medicine he experienced the advent of anesthesia, asepsis, the germ theory of disease, diphtheria antitoxin, the X-ray, and other revolutionary changes. His rise from humble immigrant beginnings to a high position in the Navy, shows that he must have been a man of considerable abilities.

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Policy

The U.S. Navy Medical News Letter is basically an official Medical Department publication inviting the attention of officers of the Medical Department of the Regular Navy and Naval Reserve to timely up-to-date items of official and professional interest relative to medicine, dentistry, and allied sciences. The amount of information used is only that necessary to inform adequately officers of the Medical Department of the existence and source of such information. The items used are neither intended to be, nor are they, susceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

Change of Address

Please forward changes of address for the News Letter to Editor: Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 20390 (Code 18), giving full name, rank, corps, old and new addresses, and zip code.

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The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

TREATMENT FOR WHITE PHOSPHORUS BURNS

The following comments by CDR C. E. Brodine MC USN, NMRI, Bethesda, Maryland, and CAPT T. H. Wilson Jr. MC USN, USNH, Bethesda, Maryland, are in answer to a report submitted recently that white phosphorus and/or copper sulfate (when used in the treatment of white phosphorus burns) may cause a hemolytic diathesis.

. . . The pathogenesis of the hemolytic diathesis . . . referred to . . . is difficult to comment on, without more detailed information. I have made a brief review of the literature and have not found any reference to a hemolytic diathesis associated with white phosphorus burns. However, a recent article in the *New England Journal of Medicine,* (Neil A. Holtzman, Donald A. Elliott and Richard H. Heller: Copper Intoxication, Vol. 275(7):347–351, Aug. 18, 1966), reports the occurrence of hemoglobinemia, hemoglobinuria, and oliguria following the use of copper sulfate in the treatment of a body burn not due to white phosphorus. There are a number of articles in the literature which document the occurrence of hemolytic anemia associated with the ingestion of copper sulfate.

The mechanism responsible for hemolysis in cases of copper sulfate poisoning remains obscure. Studies reported by Mitol *et al* suggest a possible relationship between erythrocytic glutathione and glutathione stability to acute copper sulfate poisoning. On this basis, individuals with glucose-6-phosphate dehydrogenase deficient red cells (approximately 10% of the Negro population) would be particularly prone to develop hemolysis on exposure to copper sulfate. The simultaneous exposure to Primaquine or D.D.S. would enhance the toxic hemolytic effect of copper sulfate. Critical factors that determine the extent to which copper cations diffuse into the circulation would be the size of the burn wound, percent concentration of the copper sulfate solution used and the length of time the solution is used. The possibility of over treatment with copper sulfate, i.e., use of copper sulfate for more than just a few minutes or repeated application may be a significant factor.

The problem unique to white phosphorus burns is the retention of highly reactive white phosphorus particles in the burn area with

(1) continued burning or smoldering of the phosphorus in the burn wound;

(2) absorption of phosphorus acid and phosphoric acid which result from the oxidation of elemental phosphorus in the burn wound;

(3) absorption of elemental phosphorus which is very toxic (50 mg is a lethal adult dose).

Copper sulfate has been recommended for initial treatment of white phosphorus burns in concentrations of 1 to 5% following immersion of the burn area in water. The copper sulfate reacts with the oxidation products at the surface of the phosphorus particle to form a protective coating of black cupric phosphate around the particle which is then removed.

I am not aware of any published reports on the use of 0.5% silver nitrate solution for the initial treatment of white phosphorus burns. From a theoretical standpoint, silver nitrate should be an effective agent. The silver phosphate precipitate coating the particles would turn dark with exposure to light and allow for their identification and removal. However, the silver nitrate would darken the surrounding tissue to some extent as well and it may be difficult to identify the phosphorus particles in the light. Uncoated particles would be luminous in the dark. Prolonged use of 0.5% silver nitrate in the treatment of burns may cause serious electrolyte disturbances.

The ideal agent for initial treatment would be one which would oxidize the elemental phosphorus, neutralize the reaction products and not cause further damage to the tissues. There is a need for basic research to provide an improved agent for the initial treatment phase. The practical problems and hazards of working with experimental white phos-

phorus burns are considerable, but the possibility of investigating this problem at NMRI is being explored.

There are some obvious questions that must be answered concerning the use of copper sulfate for the initial treatment of white phosphorus burns. The potential risk of systemic phosphorus poisoning if copper sulfate is not used should be defined. I would advise that the use of copper sulfate should be carefully controlled or discontinued until these questions can be answered and that a clinical trial using 0.5% silver nitrate solution as initial treatment with careful documentation of the results should be considered.

Provision should be made for collecting data on the treatment of white phosphorus burn casualties and a technical bulletin on this subject should be published as soon as the above questions are answered.—CDR C. E. Brodine MC USN.

CAPT Wilson has this to say:

Copper sulfate, absorbed via a wound, can cause hemolysis. White phosphorus, when absorbed, may produce a toxic hepatitis, which may, if severe, cause hemorrhagic tendencies. The important points in caring for white phosphorus burns include:

a. Exclude the phosphorus from contact with air. This can be done with a wet compress. It does not have to be copper sulfate, which changes only the contacting interface between the solid phosphorus and the copper sulfate pad, but does nothing to the deep portion of the material.

b. Remove all phosphorus particles as early as possible, picking out gross pieces and removing the rest with wound debridement.

I believe the use of copper sulfate is not a necessity and is potentially harmful.—CAPT T. H. Wilson Jr., MC USN.

VENTILATORY CAPACITY IN YOUNG ADULTS WITH A HISTORY OF ASTHMA IN CHILDHOOD

R. H. Trefor Jones, MB CH. B DCH; R. S. Jones,† MD MRCP DCH*
Brit Med J 2(5520):976-978, October 22, 1966.

This study was carried out in order to determine the ventilatory capacity of a group of young adults who had suffered from asthma in childhood but who had been free of symptoms for an average period of six years at the time of the study (range from four to ten years).

The results were compared with those of a group of 24 healthy adults of similar age who were divided into smokers and non-smokers, and also with a group of young adults who had continued to suffer from asthma since childhood.

Method

Selection.—The normal subjects were medical students who had no history of asthma or hay-fever. The group studied were university students who were interviewed with the cooperation of the University of Liverpool Student Health Service. All those who were recorded as having suffered from asthma as children and who had been free from symptoms for a period of at least three years were asked to participate. The adults with asthma were referred from a chest clinic in the city and were considered clinically to have moderately severe asthma.

Ventilatory capacity was assessed by determining the forced expiratory volume in one second ($F.E.V._1$) and the forced vital capacity (F.V.C.) (Tiffneau *et al.,* 1947). The effects on the $F.E.V._1$ of long exercise (8 to 10 minutes) and subsequently of isoprenaline inhalation was observed (Jones *et al.,* 1962, 1963).

Eight resting values of $F.E.V._1$ and F.V.C. were first determined with a modified Gaensler spirometer (Gaensler, 1951; McKerrow *et al.,* 1960). The mean value of the last five estimations was taken as the resting level.

The subjects then exercised by running along a covered corridor for a period of 8 to 10 minutes. At the end of this time the $F.E.V._1$ and F.V.C. were determined at one-minute intervals in order to observe the fall. (We have found that the maximum

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fall in F.E.V.$_1$ occurs usually during the first 10 minutes after the end of exercise.)

When the post-exercise F.E.V.$_1$ approximated the resting level the subject inhaled a solution of 1% isoprenaline sulphate by the method outlined by Jones (1966). At the end of this time the F.E.V.$_1$ was determined at intervals of one minute until the maximum rise was obtained.

The subject then sprinted for one minute and the F.E.V.$_1$ was repeated at one-minute intervals for 5 to 10 minutes or until an obvious maximum level had been obtained.

Results

The fall in F.E.V.$_1$ after long exercise and the rise after isoprenaline inhalation and short exercise serve as an indication of the degree of both bronchoconstriction and bronchodilatation which occurs under these circumstances (Drutel and Dechoux, 1952; Engström *et al.*, 1959; Capel, 1959; Jones *et al.*, 1962, 1963; Capel and Fletcher, 1964).

The sum of these values in litres, when expressed as a percentage of the predicted normal F.E.V.$_1$ (determined from a nomogram—Kory *et al.*, 1961), is an index of bronchial lability and may be termed the lability index.

$$\text{Lability index} = \frac{\text{Fall in F.E.V.} + \text{Rise in F.E.V.}}{\text{Predicted normal F.E.V.}} \times 100$$

Normal Group

The mean resting F.E.V.$_1$ for this group was slightly higher than that predicted from the nomogram used (mean F.E.V.$_1$ = 4.51 litres, predicted normal = 4.19 1.). After long exercise the mean F.E.V.$_1$ fell by 140 ml. (3.4%). After isoprenaline and short exercise it rose to a level 240 ml. (5.8%) above the resting level. This gives a lability index of 9.2 for this group.

When the results in those who smoked were compared with those in the non-smokers certain slight differences were noted. Both groups had the same mean age and height and hence the same predicted normal F.E.V.$_1$ (4.19 1.). The mean resting F.E.V.$_1$ in the smokers was 120 ml. less (2.9%) than in the non-smokers, and on long exercise the F.E.V.$_1$ fell by 180 ml. as compared with 100 ml. in the non-smokers. The rise above the resting level after isoprenaline and short exercise was 220 ml. in the non-smokers and 240 ml. in the smokers. Hence the lability index in the smoker was slightly higher than in the non-smoker.

The lability index of the group as a whole is similar to that found in normal children. One of the smokers had a lability index of 20, but all the others were below 15. The highest index in the non-smokers was 15, and the remainder, except for two with an index of 11 and 12, were below 10.

The F.E.V.$_1$/F.V.C. ratio in this group was above 85% in all phases of the experiment.

Adults with a History of Asthma

The results in this group are given in Table I, (not shown). The mean resting F.E.V.$_1$ was 3.93 1., while the predicted normal for their mean age and height was 4.38 1. The mean resting F.E.V.$_1$ was therefore within the normal range at 88% of normal. The mean resting F.E.V.$_1$/F.V.C. ratio was 75%.

After long exercise there was a considerable fall in F.E.V.$_1$ to a mean of 2.69 1., indicating a drop of 1.24 1. below the resting level. There was also at this stage a fall in the F.E.V.$_1$/F.V.C. ratio to 60%.

Following isoprenaline and short exercise there was a rise to 4.27 1., which was 340 ml. above the resting F.E.V.$_1$. Hence the maximum F.E.V.$_1$ attained at the end of the experiment was about 97% of normal. The F.E.V.$_1$/F.V.C. ratio at this time was 78%. The lability index for the whole group was 38.

Adults with Asthma

The mean predicted normal F.E.V.$_1$ for this group was 4.19 1. However, the mean resting F.E.V.$_1$ was only 2.39 1. (57% of normal). After exercise the mean F.E.V.$_1$ fell to 1.35 1. (actual fall of 1.04 1.) and after isoprenaline and short exercise rose to 3.27 1., which was 880 ml. above the resting level.

The F.E.V.$_1$/F.V.C. ratio at rest was 65%, but after long exercise it fell to 50%. At the end of the experiment the mean ratio was 72.5%.

The lability index for this group was 46.

The results in this group are given in Table II (not shown). Table III (not shown) summarizes the mean values found in all the groups. A diagrammatic comparison is shown in Fig. 1 and in Fig. 2 (not shown) one individual from each group has been selected and matched for age, height, and predicted normal F.E.V.$_1$.

Discussion

Normal Group

It will be seen from the results that the lability index in this group was 8 for the non-smoker and 10 for the smoker.

The resting F.E.V.$_1$ in the smokers was slightly lower than in the non-smokers, although the mean was above the predicted normal. There was a greater fall in F.E.V.$_1$ after long exercise in the smoker and a correspondingly higher rise after isoprenaline and short exercise.

The lability index for the two groups as a whole was 9, with a range of 5 to 15 in non-smokers and 5 to 20 in smokers. These values are similar to those that have been found in normal children

Adults with a History of Asthma but Symptom-Free

Many follow-up studies of asthma from childhood into adult life have been carried out, and the number of patients who were symptom-free at the time the studies were undertaken varied from 30 to 50% (Bullen, 1929; Rackemann and Edwards, 1952; Engström and Kraepelien, 1957; Ryssing, 1959; Johnstone and Crump, 1961; Ogilvie, 1962; Ryssing and Flensborg, 1963).

Some of these studies were retrospective surveys and gave an indication of the prognosis of asthma; others were performed to assess the benefit of therapy. A physiological assessment of young adults who have either "grown out" of their asthma or who have improved after treatment does not seem to be recorded in the literature.

In the series carried out by Ryssing and Flensborg (1963), of 442 asthmatic children 37% had been symptom-free for at least one year. They subdivided these into those who developed dyspnoea on effort easily and those who did not. This appears to be the only attempt to determine the status of the child cured or having grown out of his asthma, and this with regard only to dyspnoea and exercise tolerance. The absence or presence of dyspnoea is not in itself a reliable indication of the degree of ventilatory defect that may be present (Leiner *et al.*, 1965).

There appears to be reasonable agreement between different workers regarding the classification of asthma with respect to the severity of symptoms, but there is as yet no satisfactory method of correlating this physiologically. The use of F.E.V.$_1$ or the F.E.V.$_1$/F.V.C. ratio (Engström *et al.*, 1959), or the determination of peak-flow rate (Pearson, 1963), would have produced normal results in this group had they been studied at rest.

However, the determination of the airways lability by the method suggested in this article demonstrates that in this group there is a gross abnormality present which would otherwise not have been discovered.

The lability index in this group appears to bear no relation to the agents (allergy, infection, or emotion) which were thought to have precipitated the attacks of asthma. It is also unaffected by the length of history or the period of freedom from symptoms. There appears to be, however, a direct relation between the severity of the asthma as expressed by the frequency of attacks and the present ventilatory capacity as determined by the lability index—that is, the subjects who had the greatest fall in F.E.V.$_1$ on exercise were in fact those with the greatest degree of incapacity as children.

Pearson (1958), in an analysis of 625 cases, found that 47 had had periods of freedom from one to 40 years before developing a recurrence of symptoms. Rackemann (1958), in a study of 272 patients with "intrinsic" asthma, found 18 cases in which allergic asthma in young people was followed by a clear interval lasting from 10 to 30 years, during which time they were symptom-free. This period was followed later by asthma of the "intrinsic" type. In this paper and in an earlier one (Rackemann and Edwards, 1952) it is suggested that in those individuals who are not free of symptoms or who, after a period of freedom, develop a recurrence of their asthma an abnormal basic mechanism of some kind is still operating. They further suggest that the fact of long intervals of freedom between attacks makes the concept of a fundamental defect hard to justify.

Our findings have shown that the mechanism which was present during the time the asthma was active can still be demonstrated, despite the absence of symptoms. A comparison of the results in these adults with those in the children in groups 1 and 2 (Jones, 1966) shows that they conform physiologically and that their airways exhibit the same degree of lability. Engström *et al.* (1959) have shown that in the child with asthma the ventilatory defect persists despite the absence of symptoms. If the symptom-free period is therefore extended from a few weeks, as it is in the child, to years, as it is in the adult, the same abnormality persists, the only difference being that the child continues to have attacks.

It appears, therefore, that these individuals are in a latent phase of asthma and that the potential to develop a recurrence of symptoms (or the fundamental defect) is still present and may or may not be "triggered off" at a later stage by some aggravating factor.

Whether or not this mechanism was present before the onset of symptoms is of course difficult to postulate, but this could be determined by a follow-up study of children with hay-fever. It is known that 43% of hay-fever subjects will eventually develop asthma (Frankland and Gorrill, 1953). Thirteen children with hay-fever have been studied in this department and their lability index has been determined. Six were found to have an abnormally high figure. Further studies may show that those with a high lability index may be the ones who will develop asthma at a later date.

Asthma Group

In adult asthmatics the mean resting $F.E.V._{.1}$ was only 57% of normal. This confirms the fact that most of the individuals in this group had moderate-to-severe asthma and possibly also some degree of emphysema. The actual fall and rise in $F.E.V._{.1}$ in this group were similar to those found in the symptom-free group, the only difference being that the $F.E.V._{.1}$ was at a lower level.

The adults with asthma conform physiologically to those children found in group 3 (Jones, 1966)—that is, the resting $F.E.V._{.1}$ is below the normal range, the amount depending on the severity of the asthma, and the lability index is high.

Summary

Ventilatory capacity in a group of young adults who had a history of asthma in childhood but who had been symptom-free for an average period of four years was assessed by determining the changes in $F.E.V._{.1}$ which followed long exercise and subsequently isoprenaline inhalation and short exercise.

The results of this group are compared with a normal group and with a group of adults with asthma.

The changes which occur in $F.E.V._{.1}$ under these circumstances indicate the airways lability, and when expressed as a percentage of the predicted normal $F.E.V._{.1}$ may be termed the lability index.

The group under study were found to have an abnormally high lability index, indicating that some abnormal mechanism was still operating despite the absence of symptoms.

The implications of these changes are discussed, and it is suggested that adults who suffered from asthma as children but who have become symptom-free are in a latent phase of asthma. They may remain in this phase indefinitely, but they still have the potential to develop a recurrence of their symptoms.

(The tables, figures, and references may be seen in the original article.)

REMOVAL OF IMPACTED PULMONARY EMBOLI BY RETROGRADE INJECTION OF FIBRINOLYSIN INTO THE PULMONARY VEINS

REPORT OF THREE CASES AND EXPERIMENTAL STUDIES

Thomas Gahagan MD, Albert Manzor MD, A. N. Mathur MD, Carlos Grodsinsky MD, (From the Division of Thoracic Surgery, Henry Ford Hospital, Detroit, Michigan.)

Ann Surg 164(2):315-320, August 1966.

The value of pulmonary embolectomy with cardiopulmonary bypass in massive pulmonary embolism is well established. Many surgeons have carried out successful embolectomies utilizing this technic which is particularly useful in patients who develop sudden, massive pulmonary embolization following operation for an unrelated condition.

When the pulmonary artery is opened during bypass, emboli in the main vessel can be removed easily. Furthermore, fresh emboli located in distal pulmonary arteries can be removed by extraction with forceps and by Cooley's maneuver of manual massage of the lungs. Early embolectomy results are impressive even in poor-risk patients. For example, we removed large emboli from the main pulmonary arteries in an 80-year-old man within 2 hours of his collapse on the 14th postoperative day after pulmonary lobectomy. Four days after embolectomy he was ambulatory.

Other patients, however, may have multiple, smaller emboli over days or weeks which become impacted in distal branches of the pulmonary artery.

The patients may be treated for phlebothrombosis or for spontaneous or postoperative pulmonary embolization before being considered for embolectomy. In such patients, emboli impacted into the pulmonary artery branches may be impossible to remove by the most careful and systematic manual compression of the lungs. Residual emboli may produce so much obstruction to pulmonary blood flow that effective circulation cannot be resumed after embolectomy, and the patient cannot be taken off bypass.

Case Reports

Case 1. A 56-year-old very obese man was admitted to the hospital for treatment of recurrent phlebothrombosis of the lower legs. He was given Heparin and put to bed for 7 days. Swelling and tenderness greatly improved and he appeared ready for discharge when he developed sudden chest pain, dyspnea and slight cyanosis. Blood pressure, pulse and respiration were normal and the initial symptoms disappeared. Consequently, instead of embolectomy at this time, vena caval interruption with a serrated plastic clip was performed. The patient became severely dyspneic the following morning however and developed peripheral vascular collapse, and so was returned to the operating room for embolectomy. The pulmonary artery was opened and large amounts of embolic material were extracted from the pulmonary arteries. The lungs were carefully massaged and some further emboli were removed. An effective heart beat was not resumed after closure of the pulmonary artery and the patient died. Autopsy showed that the main pulmonary artery branches were clear, but peripheral branches were full of root-like fragments of emboli.

Comment. In two recent cases we have utilized a technic of injection of fibrinolysin solution retrograde into the pulmonary veins at the time of open embolectomy. Fibrinolysin was used to loosen the attachment of the impacted distal embolus to distal pulmonary arterial branches rather than to dissolve the emboli. Because the pulmonary vascular system has no valves, material injected retrograde into the pulmonary veins has access to the distal pulmonary artery through the pulmonary capillary bed.

Case 2. A 58-year-old man entered the hospital with a profound weight loss for which no cause could be found on systematic evaluation. His behavior was very peculiar from a psychiatric standpoint. He also had bilateral, large inguinal hernias. As these were the only demonstrable physical abnormalities, the hernias were repaired at a single operation. On the first postoperative day, he developed a rapid pulse and rapid respirations and the possibility of a pulmonary embolus was considered. The patient seemed to recover from this first episode, however, and although the rapid pulse rate continued he had no further breathing difficulty until the 12th postoperative day. At that time he again became dyspneic, lethargic and cyanotic. Pulmonary angiograms showed extensive obstruction of the pulmonary arterial branches on both sides, although the main pulmonary arteries were patent. Open pulmonary embolectomy was performed with cardiopulmonary bypass. Prior to manipulation of the emboli, which could be seen and palpated deep in the open pulmonary artery, a solution of 50 cc. of 5% glucose in water solution containing 50,000 units of fibrinolysin was gently injected retrograde into each pulmonary vein. After 15 minutes the veins were injected with sterile saline solution and the base of the lung was gently compressed. Repeated compression of the lung and flushing with saline brought large amounts of branched emboli from the distal pulmonary branches through the open pulmonary artery. Following closure of the pulmonary artery, heart action was good and the pulmonary artery was under no increased pressure. During closure of the chest incision, there was a transient period of increased bleeding which was thought due to absorption of fibrinolysin solution. Epsilon aminocaproic acid, 5 grams, was administered intravenously and no further bleeding was encountered. The patient's immediate postoperative condition was excellent and pulmonary angiogram made 7 days after embolectomy showed excellent filling of all the pulmonary arteries except for one basal segment branch of the right lower lobe. This still appeared to be occluded. Though the patient had no further respiratory difficulty, he died a month later. Autopsy showed cerebral cortical atrophy and dilatation of the cerebral ventricles. The pulmonary artery and its branches were free of emboli except for the residual obstruction in the single basal segment branch seen in the angiogram.

Case 3. A 59-year-old man entered the hospital for perineal prostatectomy for benign prostatic hypertrophy. He had long-standing phlebothrombosis of the legs and had been hospitalized in the past for respiratory difficulties, thought to be due to small pulmonary emboli. On the 7th day after prostatectomy, his legs became swollen and on the 11th postoperative day he had acute chest pain. Bilateral fe-

moral vein ligations were done. He then had increasingly severe dyspnea, tachypnea, cyanosis and hypotension. Pulmonary angiograms on the 13th postoperative day showed extensive bilateral pulmonary arterial obstruction. Open pulmonary embolectomy was carried out by a technic similar to that used in the previous patient with retrograde instillation of fibrinolysin. Here again, branching emboli from the distal pulmonary vessels were recovered. Epsilon aminocaproic acid was given to control excessive bleeding after protamine had been administered during the chest wall closure. Tracheostomy and ventilatory assistance were employed. Following operation, the patient made a gradual recovery and is completely well several months later.

Action of Fibrinolysin on Pulmonary Emboli

Fibrinolytic agents dissolve experimental thrombi effectively when injected in high concentration at the site of the thrombus. Systemic fibrinolysin treatment of pulmonary embolism, on the other hand, has been more difficult to evaluate because of uncertainty both of diagnosis and assessment of results. In addition time limitations are imposed by massive pulmonary embolism. Another difficulty in evaluation of thrombolytic agents in pulmonary embolus is naturally occurring spontaneous lysis. When blood clot emboli are inserted into the inferior vena cava of the dog and travel to the heart, the clots lyse spontaneously unless complete right ventricular obstruction and death is produced. Only small fragments are found in the pulmonary arteries one week later. This has been shown to occur experimentally both in systemic vessels and the pulmonary artery. Furthermore, spontaneous lysis has been shown in patients by pulmonary angiograms. We have seen and followed patients identical with those described by Sautter and coworkers in whom pulmonary emboli dissolved. Certain patients may survive acute embolism, however, only to die several weeks later from massive lung infarction with no spontaneous lysis of the original embolus. Experimentally, even in dogs which have potent circulating fibrinolysins, pulmonary emboli do not always spontaneously dissolve and in some instances cause massive lung infarction.

Experimental Studies in Dogs

Impacted Experimental Emboli

We thought that spontaneous lysis would occur less readily if the embolus were impacted into the pulmonary artery. To test this hypothesis, blood clot emboli were introduced directly into the left pulmonary artery in a series of 20 dogs and impacted to fill the branches as well as the main trunk of the vessel. Of ten animals sacrificed in 48 hours, seven had most of the embolic mass intact. Five had almost no clot lysis, the entire pulmonary artery tree being filled with embolus. The remaining 10 animals were sacrificed at intervals from 7 to 20 days. Four had significant partial lysis with only pieces or stringy remnants of the clot remaining. In the other six, however, the embolus stayed in place unlysed and with varying degrees of organization depending upon the age of the embolus. Parenchymal infarction was prominent in these six animals, two of which died of massive lung infarction in 7 and 10 days, respectively.

The degree of lysis seemed to bear no relationship to the length of time between embolization and death. The process must therefore have something to do with initial characteristics of the embolus, perhaps to the completeness of impaction at the time of insertion.

When blood clot emboli were impacted into the left pulmonary artery in four dogs and the vessel was occluded proximal to the embolus, the clot was intact 6 to 14 days later in all four animals. All had massive lung infarctions.

It is evident that spontaneous lysis occurs more readily in non-obstructing emboli when the blood stream bathes the length of the clot to effect enzymatic breakdown. On the other hand, if a vessel is obstructed proximal to the embolus, or if the embolus is impacted into a vessel having blood flowing only through its proximal end, lysis is impeded. Massive lung infarctions can be produced experimentally as late complications of extensive, completely occlusive emboli.

Removal of Experimental Emboli

In 10 dogs, 1 to 3 hours after massive embolic impaction of the left pulmonary artery, saline solution was injected retrograde into the pulmonary veins through small polyethylene tubes with the veins occluded on the atrial side. Gentle instillation of the saline solution first in lower and then into middle and upper lobe veins prolapsed the end of the embolus from the incision in the proximal pulmonary artery. Continued irrigation and gentle traction brought the embolus out intact as a cast of the pulmonary arterial tree. Small amounts of pinkish saline were sometimes recovered from the endotra-

cheal tube. No significant abnormalities were apparent in the lung. Three animals had minor residual emboli.

After impacted emboli were in place for 48 to 72 hours, removal was difficult with retrograde saline irrigation alone unless extremely high pressures were used. Preliminary instillation of fibrinolysin into the pulmonary veins (100,000 units in 20 cc. saline) partially lysed terminal extensions of the embolus or loosened attachments to the vessel wall so that saline irrigations 20 to 30 minutes later successfully ejected them. Ten animals had irrigations of fibrinolysin and saline 48 to 72 hours after embolic impaction of the left pulmonary artery. In six, sizeable emboli were removed. In one animal, a small embolus was removed while the upper lobe artery remained completely occluded. In three, no embolus was obtained and only tiny fragments were found in the pulmonary arteries, a considerable amount of spontaneous lysis having occurred.

When impacted emboli had been in place for seven days, manual compression of the lung together with fibrinolysin and subsequent saline injection were necessary for complete removal. Also in some instances it was necessary to free the proximal part of the embolus with instruments where it had become adherent to the pulmonary artery suture line. Of five animals in this category, it was possible to remove most of the emboli in four. There was severe parenchymal infarction in two animals which did not survive. Two survivors autopsied a week later had lungs which appeared normal. In two animals in this category, embolectomy was attempted by massage of the lung alone and yielded less satisfactory results than when combined with fibrinolysin and saline irrigation, as multiple distal fragments were broken off and left behind.

Between 14 to 18 days, incorporation of the embolus into the wall of the vessel and varying degrees of lung infarction made embolectomy unsatisfactory by any method.

Comment. Because of the absence of valves in the pulmonary venous system, recently impacted pulmonary emboli can be removed by simple retrograde saline irrigation of the pulmonary veins. Introduction of fibrinolysin in the pulmonary veins facilitates removal of emboli which have been in place for longer periods of time, apparently by releasing terminal attachments of the emboli.

Discussion

There are disadvantages associated with the use of fibrinolysin in pulmonary embolectomy. First, it is probably unnecessary in early embolization as the pulmonary artery can be cleared completely by simpler methods. Second, uptake of fibrinolysin into the systemic circulation after completion of bypass and reinstitution of the pulmonary blood flow causes excessive bleeding even after heparin action has been reversed by protamine. Aminocaproic acid is a specific inhibitor of fibrinolysin and is effective for this purpose, although the dose relationship of fibrinolysin and aminocaproic acid is not as well known as between heparin and protamine. Finally, introduction of solutions retrograde into the pulmonary vein, even at low pressures, in pulmonary arterial obstruction causes some pulmonary edema. This is only transient, however, and is readily treated by endotracheal suction at the time of embolectomy. Manual compression of the lung mobilizes some edema fluid into the bronchi where tracheostomy and ventilatory assistance with positive pressure facilitate its removal.

Summary

Experimental emboli impacted in the pulmonary artery tend to remain intact, become organized and cause lung infarction in contrast to non-obstructive emboli which are usually lysed spontaneously. Removal of impacted emboli was facilitated by retrograde instillation of fibrinolysin solution in the pulmonary veins followed by retrograde injections of saline. Removal of emboli by this as well as other technics becomes more difficult as the time the embolus has been in place increases.

Residual impacted emboli in distal branches of the pulmonary artery following open pulmonary embolectomy can cause persistent vascular obstruction. Retrograde pulmonary venous instillation of fibrinolysin was used in two patients with extensive embolization and in whom the embolus was impacted in the distal branch of the pulmonary artery. Fibrinolysin was helpful in these patients although side effects of excessive bleeding and transient pulmonary edema call for care in its use.

(Photographs and references may be seen in the original article.)

CLINICAL IMMUNOLOGIC STUDY OF MALIGNANT DISEASE: RESPONSE TO TUMOR TRANSPLANTS AND TRANSFER OF LEUKOCYTES

Sigmond H. Nadler MD, George E. Moore MD PhD, From the Department of Surgery, Roswell Park Memorial Institute, Buffalo, New York. *Ann Surg 164(3): 482-490, September 1966.*

For many years host resistance factors and tumor immunity have been thought to be of importance for the treatment of malignant disease. Abundant experimental evidence has accumulated over the past few years to warrant further studies in the immunologic field to determine the antigenic and immunologic properties of tumors and the possible mechanism by which the host cells may inhibit cancer cell growth or destroy cancer cells.

Evidences that host factors may be involved in the malignant process are both direct and indirect and the mechanisms are poorly understood. Existence of host resistance has been indicated by 1) occasional spontaneous regression of established tumors, 2) appearance of widespread metastases many years after apparently successful treatment of a primary lesion, suggesting that the dormancy of the cancer cells may have been controlled by the host, 3) survival of patients for long periods after incomplete removal of cancer, 4) occasional regression of metastatic disease after the primary tumor has been excised or treated, and 5) evidence that large numbers of tumor cells may be extruded into the lymphatic and vascular systems without development of metastases. It has been impossible to prove any of these factors; however, the possible existence of an immunologic mechanism requires further study.

Direct evidence has accumulated over the past few years pertaining to the immunologic properties of tumors induced in animals by chemical carcinogens and viruses. Specific antigenicity in a class of experimental tumors was first demonstrated by Foley in 1953. Using a series of tumors recently induced by methylcholanthrene in mice of the same inbred stock, he showed that the removal of a growing transplant of a methylcholanthrene-induced tumor was followed by resistance to subsequent challenge with the same tumor. The initial immunizing grafts were prevented from growing progressively by one of the following methods: 1) ligation or excision of the subcutaneous growth, 2) inoculation of tumor cells in too small numbers to produce lethal tumors, or 3) the use of heavily irradiated tumor cells which are viable but incapable of continuous division. The observations of Foley have been confirmed innumerable times and specific antigenicity has also been demonstrated in other types of experimental tumors.

Foley's technics have been extended to studying rejection of tissue grafts by transfer of homograft immunity from one animal to another by means of cells from actively immunized donors. When the donor and recipient are isogenic the transferred cells will persist and the immune state of the recipient will be sustained. In this procedure intact viable cells are required for the successful transfer of immunity. Cells from lymph nodes or spleen, thoracic duct, peripheral blood, and the peritoneal cavity have been effective in producing a state of immunity or enhanced specific reactivity to homografts upon normal recipients.

Another method of demonstrating the presence of immunologically active cells is by the subcutaneous inoculation of tumor cells that have been mixed with lymphoid and peritoneal cells into normal recipients compatible with the immune cells, the tumor cells having been obtained in suspension, i.e., ascites cells or trypsinized solid tumors. Complete suppression of the homografted tumors will then be observed.

In view of the above indirect and direct evidence of the immunologic properties of tumor in man and animals, attempts are now being made in volunteer patients with incurable cancer to determine the local and regional reactions and the clinical systemic responses to the transfer of white blood cells, particularly lymphocytes, which have been "sensitized" to a patient's own tumor.

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Method

Volunteer patients on the Chemotherapy Service at Roswell Park Memorial Institute with histologically similar incurable tumors are sensitized to each others tumor by subcutaneously implanting a piece of tumor from patient A into the thigh of patient B and vice versa, or by incubating the tumor with white blood cells cultured *in vitro*. The technics are those of accepted surgical biopsy procedures and in no instance is the well-being of a patient endangered. Following the transfer of tumor specimens from patients A to B and B to A, observations are made of the local, regional and systemic areas for specific immunologic and/or homograft rejection phenomena.

After 10 to 14 days when homograft rejection is thought to have taken place, leukocytes from patient B are transfused to patient A and vice versa; these transfusions being repeated once daily for a period of 3 weeks. White blood cells sensitized to tumor during culture *in vitro* are injected intraperitoneally in the original patient after 10 days; these injections taking place either daily or every other day.

White blood cells of those patients who have had tumor homografts are acquired by standard blood banking technics and those technics used for plasmapheresis. After 500 cc of whole blood is withdrawn from an appropriate vein into a 3-bag sterile citrated system, the blood is centrifuged and the white blood cell fraction removed. These cells are placed in a separate transfer package and transfused to the patient to whose tumor they have been sensitized; they should not be retransfused through a blood filter because of a possible loss of clumps of the cells. Plasma and red blood cell fractions of the blood removed from patients A and B are reconstituted and also retransfused to each patient, respectively, so that no anemic phenomena occur.

In those patients given white blood cells which have been sensitized by incubation *in vitro* with the patient's own tumor, the cells are harvested from the culture medium by centrifugation. They are then washed twice with phosphate-buffered saline and resuspended in the phosphate-buffered saline for patient inoculation. The cells are inoculated intraperitoneally either daily or every other day; the dose being dependent upon the numbers of cells available. We usually attempt to inoculate a minimum of one billion cells each time.

In conjunction with this study all patients are skin-tested to four common antigens, i.e., tuberculin, histoplasmin, coccidioidin and blastomycin. Skin tests are observed at 24 and 48 hour intervals to note sensitivities to any of the antigens. If a positive reaction to an antigen is obtained in a patient, repeat testing is performed in the opposite partner at the end of the study period to note whether the sensitivity has been transferred passively by leukopheresis.

Results

All patients participating in the study were required to have a histologically proved diagnosis of malignant disease and were to have been declared incurable by conventional means. A complete explanation of the method of treatment and its possible complications and/or benefits was given to the patient and his family. In all instances only those patients who volunteered to participate in the program were accepted for treatment.

Patients who had had cancer chemotherapy with any agent within 2 months prior to the date that they were scheduled to begin this program were not treated unless they definitely had shown progression of their disease in the course of therapy. Also, patients who were receiving concomitant chemotherapy or expected to undergo palliative procedures—colostomy, lysis of adhesions, radiotherapy, etc.—during the period of therapy were not accepted for treatment. Initially patients, even though they were poor risks, were accepted in the program with full awareness of the experimental nature of the program, risks involved and complications that might have ensued.

Forty patients participated in the homograft rejection portion of the project. Observations were continued for about 60 days and were considered adequate in 26 of 40 patients. Fourteen patients died within the first 4 weeks of the study, but in no instance could the procedure be considered contributory to the patient's death. Most of these patients had markedly advanced disease when started on the study.

In none of the 26 acceptable study patients did transplantation of tumor between patients cause new growth of tumor or an overt systemic reaction. The only complications following tumor transplantation were erythema and induration at the site of local implantation, occasional palpable hyperplasia of the inguinal lymph nodes, and occasional local infection phenomena at the site of homograft tumor implantation in the subcutaneous tissues of the thigh. These minor complications all disappeared within 3 weeks following tumor transplantation.

Patients were considered to have had an objective response to treatment if 1) all demonstrable disease disappeared, 2) there was at least a 50 percent decrease in the objective measurements of defined palpable masses or x-ray evidence of metastases, i.e., pleural and osseous, 3) some measurable lesions decreased significantly in size while others remained approximately stationary.

The histologic type of tumors treated are listed in Table 1.

TABLE 1. *Leukopheresis (2-15-66): Histologic Type of Tumors Treated*

Tumor	ASP*	USP**
Malignant melanoma	23	11
Sarcoma	1	2
Hemangiopericytoma	1	
Reticulum cell sarcoma		1
Breast	1	
Total	26	14

* Acceptable study patients.
** Unacceptable study patients.

Seven objective responses to treatment were noted in the 26 patients completing the course of therapy (Table 2). All responses were in the group of patients with malignant melanoma except for a partial response in one patient with breast carcinoma. The remaining 19 patients had progression of their disease and at present most have succumbed; two of these patients had a subjective response only.

In those seven patients demonstrating objective response to therapy there have been two complete responses. One patient has had a complete remission of disease for about 2 years. Three patients have had partial responses with definite decrease in the size of their tumors; these partial responses lasted for 2, 2 and 5 months, respectively. One of these patients is presently undergoing a second course of treatment; the other two patients had ultimate progression of their disease and have expired. One of the two expired patients also underwent a second course of therapy which had no further benefit. Two patients have shown a mixed type of response, with decrease in the parameters of some lesions while the remaining lesions remained about the same size. One patient received a second course of therapy with no benefit and eventually succumbed to her disease and the second patient is now undergoing a second course of treatment.

TABLE 2. *Leukopheresis (2-15-66): Response to Treatment*

Tumor	No.
Malignant melanoma	*6/23
Sarcoma	0/1
Hemangiopericytoma	0/1
Breast	**1/1
Total	7/26

* Complete—2; partial—2; mixed—2.
** Partial—1.

The only toxic responses at the time of transfusion of the white blood cells are listed in Table 3. In no instance did a patient become seriously debilitated because of transfusion reactions and in all instances the period of transfusion reaction was no longer than 2 hours.

Exposure of tumor to *in vitro* cultured white blood cells has been performed in three patients, all of whom had a diagnosis of widespread metastatic malignant melanoma. Intraperitoneal injection of the white blood cells was accomplished following exposure of the tumor to these white blood cells for 10 days. The only toxicity noted to this type of injection was a brief period of fever between 38.3 to 38.9° C and subsequent chills and in no instance was this toxicity debilitating to the patient. At present no objective responses have been demonstrated to this method of treatment.

Skin testing to four common antigens has been performed in all patients and no antigenic sensitivities were transferred.

TABLE 3. *Leukopheresis (2-15-66): Toxicity*

1. Nausea—occasional vomiting
2. Chills and fever
3. Back pain
4. Rash??

Discussion

Use of immunologic methods to treat malignancy is not new. Experiments in animal work have shown a definite immunologic basis in the treatment of certain types of animal tumors, especially those induced by chemical carcinogens and viruses. It has also become increasingly evident that tumors probably possess different antigens and will not cross react except in those tumors of viral origin.

Human experimentation has consisted mainly of the injection of *in vitro* cultured human malignant cells and autotransplantation of cells. Southam and coworkers demonstrated that injection of *in vitro* cultured cells will produce a slight antigen-antibody reaction and a local reaction at the site of injection. In some patients the tumor cell implants persisted for a few months and in some the local reaction was delayed. This was thought to be due to the simultaneous use of chemotherapy or an impaired immunologic state in those individuals who are near death from disease. These findings have been confirmed at our Institute. Autotransplantation studies demonstrated that only a small percentage, 10–20 percent of those individuals having transplantation of tumor from one site to another, will have continued growth of the transplant, despite continued growth of the original host tumor. Whether these findings are due to an insufficient number of cells being transplanted, host resistance, inability of the site of transplantation to support the tissue, or other factors is unknown. All of this previous work led to this study and its findings.

The reaction of a host to his cancer may not be an "immunologic reaction" if one limits the definition of the term to the classical reaction of antibody and antigen. The tumor cell destruction by host cells may be a direct process which "immunity" aids by strengthening cell recognition and adherence of the aggressor cell of the host to the target cell of the cancer. At present the lymphocyte, lymphoblast and plasma cell—all varient cells with some common properties—are thought by us to be the major source of aggressor cells. Much experimental work supports this.

Rosenaw and Moon devised a cell culture system for the study of the destruction of target cells by sensitized lymphocytes. They demonstrated that the lytic effect of the aggressor lymphocytes was related to functional modification of the "sensitized" cells and not to adsorbed cytotoxic antibodies.

Wilson showed that aggressor or sensitized lymphocytes must be adherent to homologous target cells in order to destroy them. Only a few percent of the lymphocytes from an immunized donor animal were capable of aggressive action. Intact aggressor cells were required for cell lysis and extracts of the cells were not deleterious to the target cells. Similarly the cytologic effects of the aggressor lymphocytes were demonstrated to be inhibited by several chemotherapeutic agents.

An extremely important observation was that non-aggressive (normal) lymphocytes or inadequate numbers of aggressive cells actually *stimulated* the growth of the target cells.

We have noted a similar stimulation of the growth of cultures of human embryonic cells to which were added non-immunized human lymphoblasts derived from human leukemia. Therefore, caution will be required lest we enhance tumor growth in patients by using impotent or too few sensitized lymphocytes.

Woodruff, Symes and Anderson reported the repression of the Landschutz ascites tumor in mice by injecting lymphocytes from rats immunized against the tumor. This heterologous assay system is interesting but probably is much less desirable than a homologous or isogenic system. It is noteworthy that the lymphocytes were capable of differential tumor cell destruction.

Mikulska, Smith and Alexander found that autografts of cancer cells would not grow in the autochthonous host if all of the primary tumor was removed and that infrequent takes would occur if a major part of the primary tumor was excised. If tumor cells were mixed with lymphocytes obtained from animals which had been immunized by exposure to irradiated tumor tissue 3 weeks earlier, growth of the cancer cells was repressed. They made the important observation that lymphocytes removed from an animal with a large tumor present failed to show antitumor activity.

These excellent studies are a prototype of the clinical studies which we are doing. Disadvantages of using cancer patients for the production of sensitized lymphocytes for therapy is apparent; for ethical reasons such donors are being used. The clinical assessment of using sensitized lymphocytes as anticancer agents cannot be considered complete until volunteer normal patients are used to produce such cells.

The studies also suggest that the most effective therapy can be expected only in patients with a minimal number of cancer cells—a suggestion which we have attempted to test in the Cooperative Adjuvant Chemotherapy Studies.

The technics developed by Klein and collaborators should be helpful in developing quantitative technics for assaying the cytotoxic effects of aggressor lymphocytes upon target tumor cells.

Moller and his wife have studied the production of antibodies *in vitro* and the destruction of target cells by lymphoid cells. Recently they suggested that nonimmune lymphoid cells could inhibit target cells in culture if they were aided by the addition of phytohemagglutin or heterologous antibodies. It was

speculated that any condition which would alter the potential aggressor lymphocytes, so that specific surface receptor sites would be formed which in turn would permit adherence to the target cells, would make possible destruction of the target cells. Apparently the Mollers have concluded informally that the cells they were using were incomplete to produce immunologic reactions of a conventional type.

We disagree with the above thesis since the cells they used were lymphocytes even if ineligible by orthodox genetic rules. We do not think that cells other than those of hematopoietic origin are capable of causing these particular reactions. It is important that all hematopoietic cells be included since we have found that both myelocytic and lymphocytic cells derived from leukemia cells (human) are capable of dedifferentiation and redifferentiation or "transformation" into cells capable of globulin production when they are cultured *in vitro*.

We have been studying the possible use of cultured lymphoblasts derived from human leukemia cells as anticancer agents. Lymphoblastic cells are cultured with cancer cells removed from the patient and subsequently reinoculated into the patient. A similar study of lymphocytes isolated from the patient, cultured and exposed to altered malignant cells before reinoculation into the host should be done.

We are aware of the deficiencies and practical problems associated with these investigations, but the rapid accumulation of new pertinent information and the development of new cell culture methods is encouraging. A final example of developments in this field is the recent report by Apffel, Arnason and Peters that treatment of cancer cells with iodoacetate may be a powerful method of inducing tumor immunity.

Results of this study tend to support the use of some type of immunologic technic in the treatment of malignancies. Whether these technics will be limited to specific histologic types of tumors or can be extended to all tumors remains to be proved. At present, methods employed in this study are of limited use and should be considered only experimental. There must be further refinement in the technics so that more beneficial results can be obtained, and methods must be developed to determine what actual processes are taking place. Whether antibodies are being formed against tumors or whether some other "anticancer" agent is being developed is not now clear but it is obvious that some mechanism has been enhanced by this method and is causing regression of tumor in a certain percentage of patients treated.

Summary

Volunteer patients with incurable cancer have been studied to determine the local and regional reactions and systemic responses to the transfer of white blood cells, particularly lymphocytes which had been "sensitized" to a patient's own tumor.

Patients with histologically similar, incurable tumors are sensitized to each others tumors by subcutaneously implanting a piece of tumor from patient A into the thigh of patient B and vice versa or by incubating the tumor with white blood cells cultured *in vitro*. Following the transfer of the tumor specimens, observations are made of the local, regional and systemic areas for specific immunologic and/or homograft rejection phenomena.

After ten to twelve days when homograft rejection has taken place, large amounts of white blood cells obtained by plasmapheresis from patient B are transfused to patient A and vice versa; these transfusions being repeated daily for a period of two weeks. The white blood cells sensitized to tumor during culture *in vitro* are injected in the original patient after ten days.

Observations of patients treated by this method are considered adequate, i.e., approximately 60 days of observation were made, in 26 patients. In seven patients with objective response to therapy there have been two complete responses, in one a complete remission of disease for about 2 years.

(The references and the omitted figure may be seen in the original article.)

PARTIAL EXCHANGE TRANSFUSION IN SEVERE CHRONIC ANEMIA

Hunter O. Cutting MD and Arthur A. Marlow MD Chicago
Arch Intern Med 117(4):478-479, April 1966.

It is foolish to transfuse a patient without blood letting, because this would not reduce the strain on the body.

Entyphronus, 17th Century.

The therapeutic dilemma presented by the chronically anemic patient was described and a solution offered in the 17th Century. Our experiences with three consecutive cases (Table, cases 1–3) in 1958 were consistent with the impression of others: (1) blood transfusions often are necessary; (2) fatal pulmonary edema may then follow. Partial exchange transfusion has offered a belated, simple, and effective solution.

Materials

All adult patients seen by the hematology service of the San Diego Naval Hospital California, between the years 1959 and 1964, were selected for treatment if they met the following criteria: (1) admission hematocrit level below 12%, (2) no prior blood replacement, (3) no evidence for significant acute blood loss, and (4) the presence of advanced age, cardiac failure, need for immediate surgery, or coexisting debilitating disease.

Methods

The head of the bed was elevated to 30°. A standard venesection was started using a vacuum bottle marked for volume. Two hundred milliliters of blood were withdrawn if the venous pressure was elevated clinically or by measurement. In the opposite arm a slow infusion of packed or sedimented cells (one unit equals approximately 275 ml) was then begun. After 15 minutes with no reaction, the infusion rate was increased. The rates of blood administration and removal were kept nearly equal after the initial deficit. The total amount administered was determined by the immediate clinical response, the hematocrit level of the venesected blood and the need for urgent surgery. The administration of each unit of packed cells required about one hour.

Results

Seven patients were treated by partial exchange transfusion (Table, cases 4–10). The outcome was uniformly satisfactory. Four patients were in overt cardiac failure and improved dramatically during the procedure. Two survived major surgery within 24 hours of admission. In five of the seven cases, the underlying disease responsible for the severe anemia was benign and correctable. This high incidence might well be expected.

Comment

Circulatory overload is considered to be a major if not the most frequent serious complication of blood transfusion. Nowhere is this more evident in the elderly chronically anemic patient with circulatory embarrassment. The administration of packed cells at a rate not greater than 1 ml/kg/hr has to some extent circumvented this problem. However in addition to the failures in our cases (2 and 3) and in those reported, this method has practical limitations:

1. The constant supervision that is necessary to detect any developing pulmonary edema and to maintain a uniform slow drip of packed or sedimented red cells over a prolonged period of time.

2. The delay in the development of evidence of circulatory overload, after the transfusion is completed.

3. The limited amount of blood that can be given safely.

Before 1962, partial exchange transfusions had been used sporadically, when Fullerton and Turner

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reported a reduction in mortality from 20% to 3% in a series of 214 severely anemic pregnant patients at term. Their technique was rather intricate and it required special equipment. Our findings indicate equally good results in chronically anemic individuals with a variety of disorders. The procedure is straightforward and the equipment is widely available.

Prestudy Patients (1-3) and Partial Exchange Patients (4-10)

Case	Age	Sex	Diagnosis	Venous Pressure *	PCV %	Ml RBC Transfused	Ml Blood Removed	Outcome
1	63	M	Pernicious anemia	Increased	12	0	0	Sudden death after 24 hr
2	70	M	Megaloblastic anemia	Normal	10	500 7 hr	0	Death in pulmonary edema, 3 hr after last transfusion
3	64	M	Hypochromic anemia; myocardial ischemia	Normal	12	350 3 hr	0	Death in pulmonary edema shortly after transfusion
4	46	M	Laennec's cirrhosis; megaloblastic anemia	280 mm H_2O	6	550 1½ hr	750	Eventual recovery (initially comatose)
5	56	F	Myxedema; pernicious anemia	Markedly increased	8	825 3½ hr	1,025	Complete recovery after 4 mo
6	22	M	Goodpasture's syndrome with uremia	120 mm H_2O	9	1,100 3 hr	1,100	Death in uremia 10 mo later (peritoneal dialysis and corticosteroids)
7	70	M	Repetitive bleeding from duodenal ulcer	Normal	8	2,650 † 7 hr	1,500	Gastrectomy 7 hr after admission; complete recovery
8	78	M	Carcinoma of rectum with complete bowel obstruction; myocardial ischemia	Markedly increased	10	1,650 5 hr	1,900	Successful surgery within 12 hr of admission (colostomy)
9	68	M	Megaloblastic anemia (malabsorption syndrome)	180 mm H_2O	9	550 2½ hr	750	Complete recovery
10	82	F	Hiatal hernia	220 mm H_2O	12	550 1½ hr	750	Complete recovery

*Peripheral.
†First 1,000 cc was whole blood.

Summary

In answer to the classical therapeutic dilemma, a simple technique of partial exchange transfusion has been used successfully in seven severely anemic adult patients.

(The references may be seen in the original article.)

MEDICAL ABSTRACTS

DERMATOSES IN VIETNAM - 1966

By LCDR John W. Curtis MC USN and LCDR T. E. Carson MC USN.

This report by LCDR John W. Curtis MC USN includes 3,500 dermatological cases seen at the Station Hospital, DaNang, Vietnam from January through December 1966. In the main, patients were young male Americans in their late teens or early 20s. The "drainage area" for this patient population began at the DMZ and ended 120 miles to the South at Chu Lai. The area is 30 to 50 miles in breadth and is tropical in climate with two seasons, dry and rainy. The monsoon season begins in October and abates in January with only periodic showers and drizzles extending into March. In July and August the temperature and humidity rise to their peaks with temperatures of 115°.

The ten most common dermatoses seen in this area in decreasing order of frequency were:

1. Dermatophytosis—pedis, cruris, corporis
2. Pyoderma
3. Miliaria rubrum
4. Verrucae
5. Pyogenic penile ulcers
6. Intertrigo, groin
7. Acne
8. Contact Dermatitis
9. Eczema
10. Urticaria

Tinea corporis was the most common diagnosis followed by Tinea cruris and pedis. Those areas in which clothing was in pressure contact with skin such as the buttocks, belt area, groin and ankles were the most susceptable to infection. The ankles and dorsum of feet were prime targets for fungus invasion. The most common fungi isolated from dermatophytosis were T. rubrum and T. mentagrophytes followed by E. floccosum. On occasion, troops were sent to the hospital for treatment because of apparent resistance to griseofulvin. However, with adequate hygiene and proper diet, there was complete clearing in 10–14 days. One percent tolnaftate solution was used locally with good response. Occasional failures about the face and neck would respond when admitted to the hospital. Apparently, profuse perspiration in the hot humid field conditions was responsible, as a mechanical factor for removal of medication.

Miliaria rubrum was extremely prevalent during the June through August period. Severe cases were admitted to air conditioned wards where cool showers and the application of mineral oil thereafter improved conditions. Occasional cases of Miliaria profunda were also seen and all were hospitalized. Generalized small white papules developed with intense "stinging" and anhidrosis. Temperatures of 102° were seen. Cool showers with air conditioning gave the only relief. Any physical activity or exposure to heat would immediately exacerbate the eruption. Hospitalization of this condition lasted from 4–6 weeks in distinction to the 5–10 days necessary for the severe Miliaria rubrum.

The combination of heat, humidity and lack of personal hygiene set the stage for the third most common dermatosis, Pyoderma. This ranged from bullous pyoderma to ecthymatous lesions of the extremities. The latter type on the dorsum of hands and extensor surfaces of the arms, represent the single most common bacterial infection and usually started as an insect bite. Indolent cases were treated with systemic antibiotics along with topical therapy. Three percent Vioform in shake lotion was more efficacious than antibiotic ointments in the Vietnam climate.

The red macerated intertriginous groin was particularly troublesome but responded to cool soaks and a steroid cream with neomycin and nystatin.

The severe cystic acne of posterior neck and back was a prime cause of medical evacuation. Both the climate and unsatisfactory personal hygiene were undoubted causes of the recalcitrance of acne, particularly the cystic type.

Most penile ulcerations were of pyogenic origin and the incidence of Syphilis was low. The occurrence of Dermatitis venenata due to vegetation was extremely low. The incidence of Dermatitis medicamentosa particularly due to nitrofurazone and Merthiolate was higher. Creosote from poles used in building piers was another frequent cause of dermatitis of the hands and arms in SeaBees.

The eczema group including nummular, flexural, and dyshidrotic types was of low incidence overall but high on the list of patients requiring evacuation out of the country. One-fourth of all evacuations out of the country for dermatological reasons was made up of this group. Of 27 cases of atopic dermatitis, 18 required hospitalization and 10 evacuation.

Urticaria was no more commonly seen than stateside. Penicillin reactions accounted for about 1/5 of the recurrent urticaria. Two dramatic cures occurred after treatment of hookworm with tetrachlorethylene. Considering the relatively large number of hookworm cases seen in the hospital, it must be considered a rare cause of urticaria. Two cases of cholinergic urticaria were seen and evacuated. A total of 55 cases of urticaria were treated with hydroxyzine with excellent control in 53 cases. The remaining 2 cases were evacuated out of the country.

The onset of the monsoon season ushers out Miliaria rubrum but in its place arrives a more debilitating dermatosis. This is the tropical or warm water immersion foot syndrome. The first of these cases was seen in November with an increasing incidence reaching a peak in January and declining in February. The sine qua non of this condition is continued contact with water. The length of time of exposure resulting in the full blown syndrome is variable, and consists of a thickened boggy and wrinkled sole followed by swelling of the feet, paresthesia, maceration and fissuring. Treatment consists essentially of allowing the feet to dry out with care of any secondary infection as required. Research is presently underway with silicon compound that is applied to the feet prior to exposure to prevent the immersion foot syndrome.

Old favorites such as creeping eruption (Larva migrans) occurred in several personnel but did not present any particular problem unless there was secondary infections. Scabies is widespread among civilians and particularly among the infants and mothers. Only 11 cases were seen among military personnel.

In reviewing the experience of the past year, it is evident that the environment plays a major role in the type and severity of the observed dermatoses. In spite of the conditions, most can be adequately treated in-country as shown by the evacuation rate of 44 patients for the entire year, (1%) of all dermatological patients. These included in order of decreasing frequency—Atopic eczema, Acne, Urticaria, and Psoriasis. These are all chronic dermatoses which do not do well in the military service and appear to be aggravated even more by a tropical climate.

(Abstracted by: CAPT J. J. Downey MC USN.)

POST-HEMIPLEGIC EPILEPSY IN THE ELDERLY

Wilfred Fine MD, Brit Med J 1:199–201, January 28, 1967.

Ten patients suffering from post-hemiplegic epilepsy are described in this report. The author divided them into two clinical categories: (1) motor manifestations; (2) sensorimotor manifestations. The former can be confused with fresh cerebrovascular accidents and the latter may have pain severe enough to be confused with pain of thalamic origin. A third clinical category is mentioned, mental manifestations, but not considered in this group. The importance of the recognition that epilepsy is not an uncommon sequel to post-thrombotic hemiplegia in the elderly is stressed. The occurrence of this condition is not necessarily indicative of a rapidly progressive lesion but means merely that a center of cerebral irritation exists which can be stimulated by fluctuating changes in the internal environment that become more extreme with increasing age owing to decreased homeostasis. These patients, in the author's experience, have responded well to anticonvulsants.

STUDIES ON INFECTIOUS MONONUCLEOSIS V. THE ARNETH COUNT (PRELIMINARY OBSERVATIONS)

LCDR E. F. Cantow MC USN and LCDR J. E. Kostinas MC USN, (From the Department of Medicine, U.S. Naval Hospital, Portsmouth, Virginia.) Amer J Med Sci 253: 119/221–122/224, February 1967.

Hypersegmentation of the neutrophils (a rightward shift) has been noted to be one of the earliest findings of a megaloblastic anemia, even precluding the eventual red blood cell depression. Herbert's criteria for the enumeration of the Arneth count is generally accepted as being the most useful to the clinician. In our studies of infectious mononucleosis, a shift to the right was noted on the peripheral blood smear. One hundred and thirty serial peripheral blood smears from 41 consecutive patients

with documented infectious mononucleosis were studied. Of the Arneth counts, 45.4% were abnormal utilizing the criteria of the increase over the normal range of four-, five- and six-lobed neutrophils. The greatest number of abnormal counts occurred late in the course from the fourth to the sixth week of illness.

A relative folic acid deficiency is postulated as the etiology of the rightward shift and possible mechanisms are discussed.—Authors' summary.

THE TREATMENT OF MALIGNANT PLEURAL EFFUSIONS BY CLOSED TROCAR TUBE DRAINAGE

C. J. Lambert MD, H. H. Shah MD, H. C. Urschel Jr. MD, and D. L. Paulson MD, (From the Department of Thoracic Surgery, Baylor University Medical Center, Dallas, Texas.) Ann Thorac Surg 3: 1–5, Jan 1967.

The authors discuss various methods of treatment of patients with malignant pleural effusions including needle aspiration alone or aspiration accompanied by inter pleural instillation of some radioactive or chemotherapeutic agent; talcum instillation with tube drainage, instillation of sclerosing agents, and thoracotomy with pleurectomy and then review a six year experience with 102 cases. Sixty-eight of these were treated with multiple thoracenteses varying from one to ten times, 22 with underwater tube drainage alone, and 12 with tube drainage as a part of open thoracotomy. Twenty of the 68 treated with multiple thoracenteses required tube drainage to rectify some complication of thoracentesis. The average hospital stay for thoracentesis alone was eight days; for tube drainage following complications of thoracentesis, twelve days; for tube drainage alone, seven days; and following thoracentesis plus tube drainage, eight days. The recurrence rate following thoracentesis was 100 percent; for tube drainage alone, 14 percent; for tube drainage after thoracentesis, 0 percent; and with tube drainage following thoracotomy, 17 percent.

DENTAL SECTION

DENTAL CORPS TRAINING

The Dental Training Committee met in the Bureau of Medicine and Surgery during the week of 10 January 1967, to recommend dental officers for advanced training in fiscal year 1968.

Recommendations for assignment were based upon indicated preferences for training, available billets that best coincided with stated preferences, seniority as related to active duty in the naval service, academic records earned during predental and dental school training, and service record.

The demand for graduate and postgraduate education continues to increase each year. The current ratio of four applicants for each billet makes it mathematically impossible to fulfill all requests. In an effort to provide advanced training for as many officers as possible, the U.S. Naval Dental Corps has progressively, each year, expanded its training opportunities.

This has been accomplished to a degree by increasing the number assigned to Graduate and Postgraduate Courses at the Naval Dental School from 28 to 32 in fiscal year 1968, by the establishment of the Postdoctoral Fellowship Program and by increasing the number assigned to long courses of instruction at civilian institutions.

Even with the above increase in the overall educational program of the Naval Dental Corps, it is regrettable that all applications for advanced training cannot be fulfilled. The Training Committee strives to distribute the training billets as equitably as is possible, for the overall welfare of the Dental Corps.

It is, and it will continue to be, our desire to increase the amount of training possible in order to meet the ever increasing demand for training and to reflect the highest degree of professional excellence attainable for the benefit of all personnel of the Navy and Marine Corps.

All applicants for graduate courses, postgraduate courses, first, second and third year level (residency) training, postdoctoral fellowships, and long graduate courses at civilian institutions, commencing

in the academic year 1968–1969, are requested to submit applications to the Bureau of Medicine and Surgery at least six weeks prior to the deadline of 1 December (MMD 6–130) to allow for possible forwarding delays and to allow sufficient time for processing of records.

In conjunction with requests for assignment to any of the above training programs, it is requested that transcripts of academic records earned during predental and dental school training be forwarded to this Bureau, Code 611, for review by the Dental Training Committee. Any charges incurred in the procurement of the requested transcripts must be at the expense of the applicant.

Additionally, it is requested that a statement concerning motivation for requesting any of the above training programs, consistent with known abilities, interests and career plan, be forwarded to the Bureau of Medicine and Surgery, Code 611.

At present there are several programs of advanced training which the applicant should consider:

1. The Graduate Courses, Naval Dental School—Principally for applicants motivated for board certification, or for subsequent graduate training in a civilian institution.

2. The Postgraduate Courses, Naval Dental School—For applicants desirous of refresher training or increased competence in general dentistry.

3. The Postdoctoral Fellowship—Principally for junior officers to obtain earlier advanced training than is possible by awaiting assignment to the Naval Dental School. A second aim of the fellowship program is the training of a broader base of specialists for the staffing of clinics not requiring board certified personnel, and research facilities operated by the Naval Dental Corps. In outstanding cases, the Training Committee may accept the fellowship as the equivalent prerequisite (MMD 6–124, 6–125 and 6–129) for advanced training in a civilian institution. Although less rigorous than a residency, fellowships have been established as academic periods of study, clinical training, or research which provide a broad base for future training for the ambitious junior officer, under guidance of an established preceptor. The fellowship does not preclude further training at either the Naval Dental School or further training at a civilian university.

Postdoctoral fellowships are available in the clinical fields of periodontics, prosthodontics, endodontics and oral surgery. Research fellowships most available are in microanatomy, biochemistry, and microbiology. Some overlapping into allied fields will, of course, occur. Thus, the research fellow would not be limited to a single discipline. His application should reflect his basic motivation.

Fellowship sites are not fixed. Those clinical activities staffed with a board qualified officer or with a diplomate of a given specialty and which have an adequate supply of appropriate clinical cases will be considered eligible. The two principal sites for research fellowships are the Dental Research Facility, Great Lakes, Illinois, and the Naval Medical Research Institute, Bethesda, Maryland. Other fellowship sites, depending on unique requirements, will be considered. Dental officers of the Regular Navy, in the ranks of lieutenant through commander, and who have completed a tour of sea or foreign shore duty and are eligible for at least one year of duty within the continental United States, may submit applications to the Chief, Bureau of Medicine and Surgery in accordance with MANMED 6–130.

4. The graduate program in endodontics, oral pathology, oral surgery, periodontology and prosthodontics is accomplished by a first year, second year or third year (when required) level of training to fulfill the formal training requirements for examination by the American Board of each recognized specialty. The first year level of training for the above specialties is primarily didactic and consists of basic science courses taken at the Naval Dental School or at an equivalent civilian university. It is a necessary prerequisite for assignment to the second year level or third year level. The second and third year level of training is offered to those officers, selected as possessing outstanding aptitude in their particular specialty. The second and third year level, which is clinically oriented, is accomplished at one of seven designated naval hospitals, the Naval Dental School, an approved naval dental activity, or at an equivalent civilian university.

5. Graduate Courses at civilian institutions are offered to satisfy part of the Navy's requirements for well trained dental officers to practice, teach, and conduct research studies in the various specialties of dentistry, and to provide the officers with part of the formal training requirements for certification by the recognized American specialty boards. The long courses at civilian institutions would be principally for second and third year level of training; however, in selected cases, a first year level may be offered to outstanding Postdoctoral Fellowship trainees or candidates with comparable prerequisites. Long courses

are also offered in selected cases for graduate training in operative dentistry, oral medicine, research, oral roentgenology, public health/preventive dentistry, and prosthodontics with emphasis on maxillofacial prosthesis.

To correct a popular misconception that exists, it should be stated that the Graduate and Postgraduate Courses at the Naval Dental School are not prerequisites for promotion, and non-selection to a course of instruction is not to be considered a reflection on an individual or his career. There are simply not enough training billets to satisfy each applicant at the specific time and place that he desires long courses of training.

It should be emphasized that the greatest requirement that the Dental Corps has is the hard-hitting, aggressive officer, well trained in all phases of dentistry who provides the general everyday treatment to personnel of the Navy and Marine Corps. Short inservice and outservice courses in the overall Training Program are designed to provide the greatest amount of training to the greatest number of personnel in order that the mission of the Dental Corps may be accomplished.

The increasingly higher level of dental health enjoyed by personnel of the Navy and Marine Corps can, basically, be attributed to the research and broad educational opportunities of the Naval Dental Corps.

CHICAGO DENTAL SOCIETY MIDWINTER MEETING

Officers from the Naval Hospital, Great Lakes, Illinois, presented the following table clinics at the 102nd Midwinter Meeting of the Chicago Dental Society at Chicago, Illinois, on 6 February 1967:

"Closure of Oral Antral Fistula"
CAPT Joseph F. Link DC USN
MAJ James W. Wooten DC USAF

"Pin Amalgam Technics"
LT Ronald S. Fenn DC USN

"Wax Added Technic for Full Coverage"
LT Robert L. Kjome DC USN

"Technics in Intra and Extra Oral Suturing"
LT R. Perry Mills Jr. DC USN

'Class III Invisible Gold Foil"
LT Mark E. Simons DC USN

NURSE CORPS SECTION

NURSES NOTES FROM THE USS REPOSE

The following excerpts have been taken from communiques received from the USS REPOSE from May of 1966 to the present date.

July 1966

During July the REPOSE went to Subic Bay and replenished fuel and supplies, leaving there for Vietnam on 15 July. On 17 July she arrived on station off the coast of Hue-Phu-Bai area. GEN Lewis W. Walt USMC came on board to brief the hospital staff on Operation Hastings.

On 18 July the first casualties were received from the battlefield. In the first two hours 12 casualties requiring immediate surgery were received and sent directly to the operating room. Within the following nine days approximately 200 casualties were admitted. The highest number of admissions per 24-hour period reached 72. Three operating rooms functioned continuously for five days completing major surgery on 79 patients. Unlike previous casualties, the majority of injuries were due to sniper fire and included abdominal and sucking chest wounds. Other wounds were due to multiple shrapnel fragments necessitating several surgical procedures on the same patient. The full gamut of technical equipment from chest pumps, to Bird respirators, to Hypothermia blankets, and the decompression chamber was employed during this period.

Medical patients presented no less a challenge than the surgical problems, with numerous diagnoses of malaria and fever of undetermined origin. These patients require meticulous nursing care—frequent observation, vital sign checks, intake and output records, adequate fluid intake, and timely administration of medication. Several of the malaria patients with elevated temperatures of 105 to 106 degrees Fahrenheit failed to respond to aspirin and alcohol sponges and necessitated the use of the hypothermia blanket. Nursing activities during Operation Hastings were demanding, but extremely rewarding. Many additional off duty hours were spent on the wards to ease the burden of mass admissions.

The recovery room, used also as a preoperative staging area, placed additional heavy demands upon nurses and corpsmen. Of particular notice was the exceptional performance of the corpsmen who so diligently attended to casualties and matched the nurses in extra duty hours. Their exemplary conduct was an inspiration to all of the nurses on board.

August 1966

On station for almost the entire month, spending Saturday to Wednesday at DaNang and Thursday and Friday at Chu Lai.

The wards were busy with a steady influx of patients. Occasional periods brought mass casualties, depending on the degree of action ashore, and especially at night when the Viet Cong are most active. Professionally, as nurses, we were proud to have been a part of another first—open heart surgery performed for the first time at sea and in a war zone. Our patient was a sixteen year old Vietnamese girl, Phan Thi Truong. She was brought aboard with other Vietnamese civilians for possible corrective surgery as part of our People to People Program. The girl suffered from a defective mitral valve resulting from rheumatic fever. The stenosis of the valve was repaired during surgery while she was on the portable heart-lung machine for a total pump time of nineteen minutes. Postoperatively, she was cared for in the Intensive Care Unit for four days and then was transferred to the International Ward for another two months of follow-up care. The personnel caring for her were fast to learn a few words of Vietnamese in order to communicate with her. Such words as "ho" (cough), "dao" (pain), and "nunc" (water) were useful during her postoperative days. Phan Thi Truong's heart is now number one and she was the number one experience in this field. Those who attended her will not soon forget the beautiful young Vietnamese girl who was helped to a more hopeful future.

A few days later, we received five Vietnamese civilians who were injured in the bombing of a village restaurant; all arrived simultaneously and all required craniotomies. Also during this month, several cases of Bubonic Plague were identified among villages in the vicinity of Chu Lai, thanks to the assistance of our laboratories facilities including FAST (Fluorescent Antibody Staining Technique).

During August the "Big Race" or "Lip Sweepstakes" was held. This was a race between teams of Hospital and Ship's Company personnel, using six of the REPOSE lifeboats and was held for the benefit of LIP, an eight year old Vietnamese boy. He was the first Vietnamese patient to be admitted to the REPOSE. An orphan, blind from cataracts, he was aboard for over three months after corneal transplantation. The Navy Nurse Corps was represented in the officers' boat by a most hardy rower, LT Rosemary Geraghty. The race was won by the crew from the Engineering Department and unfortunately, the officers came in last.—Nursing Div, BuMed.

GRADUATION OF INDOCTRINATION CLASS N–705 NEWPORT, R. I.

On 5 February 1967, the U.S. Naval Schools Command, Newport, Rhode Island, graduated members of the Nurse Corps Indoctrination Class N–705. Forty-four nurses completed the course, preparing them for the demanding responsibilities of Nurse Corps officers.

Guest speaker for the graduation ceremonies was VADM John S. McCain Jr. USN, Vice Chairman, U.S. Delegation, United National Military Staff Committee. LT Peggy R. Self NC USNR, from Haughton, Louisiana was elected to speak for the Nurse Corps/Medical Service Corps Class.

On 2 February 1967, at Color Girl ceremonies, Mrs. Harold McCormick, President, Women's Division of the Newport County Chamber of Commerce presented the honor award to LTJG Johanna D. Christensen NC USNR from Spokane, Washington in recognition of her achievement in academic and military subjects which placed her first in the class.

A Leadership award was presented to the student displaying outstanding personal example and sense of moral responsibility. Mrs. Michael Curran, President of the Aquidneck Business and Professional Women's Organization made the award to LT Peggy R. Self NC USNR, from Haughton, Louisiana.

Following the graduation ceremony, a coffee was held at Nimitz Hall.

LT Self and LT Christensen are assigned to the U.S. Naval Hospital, Camp Lejeune, N.C.—Nursing Div., BuMed.

Graduated Members of the Nurse Corps Indoctrination Class N–705

—Official U.S. Navy Photograph

Back Row: Bernard; Boddiford; Budnick; Cayton; Christensen; Cordes; Davies; Dupont; Everett;Fetters; Fisher; Flippens; Franklin; Gilmour; Gulbransen. *Middle Row:* Hare; Hiller; Howe; Hrisides; Irving; Jennings; Jones; Kirk; Kondash; Lane; Loughran; Masters; McLane; Murphy; Oravec; Osteen; Parsons; Roberts. *Front Row:* Ryan; Self; Sorensen; Spivey; Stilwell; Taylor; Tiemann; Warren; Wiggins; Withers; Wright.

OCCUPATIONAL MEDICINE SECTION

ACUTE OCCUPATIONAL CADMIUM POISONING

A CRITICAL REVIEW OF THE LITERATURE

LCDR Barry Dunphy MC USN, Virginia Beach, Va.,
JOM 9(1):22-25, January 1967.

The recognition of cadmium as a contaminant in certain zinc ores led to its identification as a chemical element in 1817. The world's annual production of cadmium amounts to about 10,000 tons, of which about 50% is used for electroplating, and most of the remainder used in the production of cadmium alloys. In respect to acute occupational exposures, the most important physical properties of cadmium compounds are their low melting points and insolubility in water.

Occupational Exposure

In this country occupational exposure to the fumes of cadmium was infrequent until after World War I, when cadmium electroplating was introduced. In 1925 animal experiments suggested the possibility of a respiratory hazard associated with acute occupational exposures. Subsequent industrial experience soon confirmed that melting cadmium or cadmium compounds without adequate ventilation was an extreme occupational hazard. Indeed, their

toxicity was so great that freshly generated cadmium fumes received consideration as a chemical-warfare agent.

In 1962 the U.S. Public Health Service listed the following occupations as potentially hazardous:

Alloy making
Aluminum solder making
Cadmium compound collecting-bag cleaning
Cadmium compound collecting-bag handling
Cadmium plating
Cadmium smelting
Cadmium vapor-lamp making
Cadmium working
Ceramic making
Dental amalgam making
Electric instrument making
Electroplating
Engraving
Glass making
Incandescent lamp making
Lithography
Lithopone working
Metalizing
Paint making
Paint spraying
Photoelectric cellmaking
Pigment making
Small arms ammunition making
Smoke bomb making
Soldering
Solder making
Storage battery making
Textile printing
Welding, cadmium alloy
Welding, cadmium-plated objects
Zinc refining

Pathology

Knowledge of the pathology of acute poisoning from occupational exposure to cadmium fumes is based upon fatal cases in humans and upon animal experimentation. In contrast to other forms of cadmium poisoning, the respiratory system is the only organ system significantly injured.

The respiratory system manifests a characteristic pattern of injury response to cadmium that can be divided into three overlapping phases: edematous, proliferative, and fibrogenic.

The edematous phase begins during the period of exposure, reaches its peak within 4 to 48 hr., and begins to diminish within 72 hr. This phase represents the initial inflammatory response to cadmium of some 55 sq. m. of irritated pulmonary membrane, and is similar in nature to that produced by other deep-lung irritants. A rapid interstitial extravasation of fluid from an inflamed pulmonary capillary bed results. Often the interstitial edema develops so rapidly that it causes a complete separation of entire intact sheets of pulmonary epithelium from its underlying stroma. As the interstitial tissues become progressively distended, the accumulating fluid eventually escapes into the alveoli; this may then be followed by the precipitation of fibrin.

The proliferative phase begins within 72 hr. of exposure and continues for about a week or 10 days. This phase represents the most striking response of the pulmonary system to an acute cadmium insult. Not only is there thickening and edema of the alveolar septa associated with a cuboidal metaplasia of the alveolar epithelium, but there is also proliferation of histiocytes and reticular stroma to produce polypoidal lesions which in some cases virtually obliterate alveoli and result in what has been termed a "proliferative interstitial pneumonitis".

The fibrogenic phase has been observed in approximately 25% of experimental animals surviving severe acute cadmium exposures, and, occasionally, among human survivors. The resultant pulmonary fibrosis has a peribronchial and perivascular distribution, which later could be associated with some minor pulmonary disability.

Signs and Symptoms

Because of individual differences and varying circumstances of exposure, some latitude of opinion about the signs and symptoms of acute occupational cadmium poisoning appears in the literature. The data used in Table 1 were drawn from 50 of the reported cases.

TABLE 1. Signs and Symptoms of Acute Cadmium Poisoning

Sign and/or symptom	% of cases in which manifested	Mean time of onset (hr. after exposure)
Nasopharyngeal irritation	51	4-8
Chest pain	51	24-36
Headache	34	6-10
Dizziness	34	6-10
Cough	30	20
Dyspnea	26	30
Vomiting	23	10
Nausea	23	10
Chills	13	10
Weakness	12	6-24
Diarrhea	7	10

If they do nothing else, these figures underscore the complete absence of significant immediate symptoms that can serve to warn workers that they are receiving a hazardous exposure. Of some interest in this connection is the fact that certain workers complained of an unpleasant metallic taste in the mouth, accentuated by cigarette smoking, during, or immediately after, their exposure.

Most nearly typically, following a latent period of 4 to 10 hr., the first premonitory symptoms of nasopharyngeal irritation, headache, nausea, vomiting, weakness, chills, and diarrhea are initially interpreted by the poisoned worker as either "flu" or some manifestation of metal-fume fever. In this regard, some long-term welders have described their initial symptoms as identical to those of "brass chills," except that on previous occasions they had never noticed accompanying chest pain. This point may be of some value when attempting to make an early differentiation between the 2 disorders. It must be recalled that the onset of chest pain is often delayed until 24–36 hr. after exposure.

The premonitory symptoms, which are virtually identical to those associated with metal fume fever, and probably produced by an identical protein-denaturative mechanism, blend with the merging symptoms of pulmonary involvement, and then disappear. When the rate of fluid loss into the pulmonary interstitium is rapid, the resultant hemoconcentration produced may be aggravated by the preceding vomiting and diarrhea of the premonitory period.

In the early stages of emerging pulmonary symptoms (corresponding to the edematous pathological phase), the diffusion and pulmonary-exchange rates of carbon dioxide are less impaired than are those of oxygen—this because of relative differences in their plasma solubilities. Consequently, an ashen-gray cyanosis without associated dyspnea is frequently seen. During later stages (corresponding to the late edematous and proliferative pathological phases) progressive interference with the diffusion and ex- of both gases produces the purple cyanosis and extreme air hunger characterizing the classical picture of suffocation.

Because of the predominantly interstitial location and fibrinous character of the fluid accumulating in the pulmonary parenchyma, physical examination of the chest has tended to reveal little indication of the catastrophic events occurring within the victim's chest until he is near death, when moist rales and rhonchi become evident. Roentgenographic examination of the chest, most often revealing numerous scattered patchy bronchopulmonary infiltrates, has been useful in many of the cases reported.

In the majority of cases hyperpyrexia was not prominent, except in the premonitory period, in the event of a superimposed bacterial infection, or in the agonal phases of a terminal case.

Diagnosis

Antemortem diagnosis rests primarily upon a clinical suspicion that acute occupational cadmium poisoning has occurred in any cadmium-exposed worker manifesting symptoms suggestive of metal fume fever, and an appreciation of the significance of associated chest pain, dyspnea, or cyanosis in such individuals. The need for careful observation and x-ray examination of the chest in such cases is obvious.

Prognosis

Since the case fatality rate for acute occupational cadmium poisoning ranges between 15 and 20%, the initial prognosis for recovery should be guarded. The longer the latent period before the onset of premonitory symptoms, and the longer the time required for the appearance of symptomatology referable directly to the pulmonary system, the better the prognosis. Any worker manifesting premonitory symptoms during, or immediately after, exposure and chest pain or other pulmonary symptoms in less than 12 hr. of exposure should be considered to have a grave prognosis for life. Sustained hyperpyrexia is associated with a less favorable prognosis.

The probability of death decreases as the patient progresses through the edematous to the proliferative and fibrogenic phases. The majority of deaths occur within the first 7 days after onset of symptoms. Recovery in nonfatal cases is rapid and generally occurs between the seventh and eleventh day. Usually the chest film appears normal within 4 weeks, and recovery is uncomplicated.

The urinary excretion of cadmium bears no known relationship to the severity of the acute poisoning, to the duration of exposure, or to the physical state of the exposure material; it is merely a confirmation of absorption.

Prevention

Consideration of the circumstances and events surrounding cases of acute occupational cadmium poisoning reported in the literature reveals that three factors are common to most of them. First, the pres-

ence of cadmium in some particular alloy or on the surface of some other metal is unsuspected. Second, some physical or chemical process (i.e., heating, spraying, brazing), capable of generating high concentrations of particles smaller than 10μ in diameter, is in use. Third, sufficient ventilatory protective measures are not provided.

Preventive measures must be directed primarily at the third factor if cadmium poisoning is to be eliminated.

Treatment

Any patient for whom this diagnosis is entertained should be hospitalized immediately and adequate intensive therapy should be instituted at once. Simultaneous attention should be given to combating the fulminant interstitial pulmonary edema, which can be anticipated, and to the early mobilization and elimination of cadmium from the patient's body by the following measures.

1. While it has been stated that the use of EDTA appears preferable to BAL, MacFarland's experimental studies suggest that BAL may be real benefit if given promptly following exposure, and the question requires further evaluation.

2. Early "elective" tracheostomy utilizing a large cuffed endotracheal tube is preferable to "emergency" tracheotomy at a later date.

3. Intermittent positive-pressure breathing has been recommended to insure delivery of 100% oxygen under pressure, with nebulized bronchial dilators and other local therapy, such as surfactants, when they appear to be indicated. It should be pointed out, however, that absolute bed rest is usually prescribed, and the use of intermittent positive-pressure breathing may be expected to require significant energy expenditure on the part of the patient. Its use, thus, requires good clinical judgment. In this regard good data are not presently available to demonstrate that intermittent positive-pressure breathing offers significant advantage over 100% O_2 at atmospheric pressure. Humidified oxygen is recommended in either case to prevent excessive drying effects.

4. It has been suggested that morphine has been most effective in relieving early anxiety and combating tachypnea, both of which are, of course, desirable; however, others (including Frederik C. Christensen and Ernest C. Olson) have associated occurrence of death with use of morphine in such cases. Sudden death may, of course, be expected to occur in such cases without implied drug effect; however, the most careful clinical judgment and observation is required in the decision to use morphine. Some believe that its use in such cases is contraindicated. This is another area in which good data are not available, and better recording and reporting are needed.

5. Aminophylline used intravenously will decrease bronchospasm and increase cardiac output; however, there are no data to suggest that it is more effective than nebulized bronchodilators, and the latter would appear to offer less hazard than the intravenous route, from the standpoint of producing potentially serious side effects.

6. High doses of steroids appear to have been effective in preventing bronchiolitis obliterans, a fatal complication in a significant number of such cases. These are best used where there is definite clinical evidence of troublesome or recurrent pulmonary edema and, in such cases, should be initiated on or about the third day and continued under careful medical supervision until the patient is out of danger. Their routine use in all cases suspected of overexposure is not recommended because of the potentially serious side effects of steroid therapy.

7. While heart failure will require utilization of appropriate therapy, including rapid digitalization, it should be recognized that the pulmonary edema which presents originally is not of cardiac origin. Routine use of digitalis is, therefore, not recommended.

8. Prophylactic use of the broad-spectrum antibiotics has been recommended, but there are no good data to show its value in effecting reduced morbidity or mortality in routine use.

In all of the above therapeutic considerations, it is essential for the attending physician to follow the cases carefully and with considerable attention to the patient's symptoms, recording and reporting therapy used and its results as well as possible. From such data should eventually be developed validation of therapeutic procedures.

INDUSTRIAL HYGIENE PROBLEMS WITHIN RESEARCH LABORATORIES

P. G. Rentos MPH, Salt Lake City, Utah and E. J. Baier MPH
Harrisburg, Pa., Public Health Rep 82(1), January 1967.

Traditionally, industrial hygiene has been associated with the evaluation and control of environmental stresses within manufacturing industries. Manufacturing processes are studied individually, contaminants are isolated, the degree of hazard is measured, and unnecessary or hazardous exposures are controlled. Today, the industrial hygienist faces new problems such as exposure of people to noise, microwaves, laser and maser radiations, and to propellants and chemicals used to eliminate plant fungi from the nose cones of space-exploration vehicles. The search for specialized technical knowledge is, as never before, a necessary and continuing process.

Research installations afford fertile grounds for study which can provide a better understanding of the future industrial health problems in their formative stages.

Evaluation of Research Installations

Industrial research installations employ a highly trained technical staff representing a substantial investment. Recognizing the need to serve the worker irrespective of his place of employment, the division of occupational health of the Pennsylvania Department of Health conducts comprehensive evaluations of such installations. The purpose of such study is twofold, namely, to assess the character of operations in terms of immediate hazards to research personnel and to gain knowledge about future stresses and air-contamination hazards in the manufacturing and service industries. The research installations fall conveniently into two categories—those engaged in pure research and those performing research for improvement of, or in connection with, a manufactured product.

Hazards Uncovered

The industrial research complex in Pennsylvania is of significant size. In 1963, approximately 629 industrial establishments were actively engaged in some form of research. Research directors and personnel in these establishments generally have advanced degrees and are familiar with work hazards, but they are not always familiar with proper safety and industrial hygiene techniques. Most take adequate precautions, but some regard exposure to gases like hydrogen sulfide or sulfur dioxide as harmless. Mercury contamination on the laboratory bench and floor is, on occasion, taken for granted. In one instance, a chemist with a doctorate degree was not aware of the hazards associated with the carcinogen, betanaphthylamine. On the other hand, the business manager of the same installation, who did not profess to be familiar with chemistry, was aware of the dangers. At another site a scientist contracted a severe dermatitis from handling acetone while preparing samples for observation with an electron microscope. This man was proud of his knowledge of the dangers of ionizing radiation, but he did not know that acetone could harm his skin.

At one location, graduate engineers designed custom electroplating plants. Using glass tanks, the engineers arranged plating baths on the floor in various configurations until the best material flow was achieved. Then varying strengths of solution and plating amperages were tried until a proper plating thickness was obtained. These operations were performed in a room about 10 by 20 by 10 feet, cluttered with rusty pipe, corroded tubing, and contaminated tools. Since there was no exhaust ventilation, the mists that formed resulted in eye irritation and a choking sensation. Such a condition would have caused workmen complaints in many manufacturing plants.

Highly trained research personnel are not oblivious to health hazards. They would be the first to confess that a certain technique causes severe headache or sneezing. A few are likely to ignore symptoms because they become so absorbed in what they are doing. They admit that they should take proper precautions. Because their experiment is progressing so well, they simply do not take the time. Once these research personnel are made aware of hazards, they become proponents of good hygienic practice, seeking the industrial hygienist's advice to help solve their problems.

A second kind of laboratory employee is the highly skilled technician assisting in advanced research.

This employee is frequently unfamiliar with the toxic properties of the chemicals he is handling. On a visit to a chemical research laboratory, we found a technical-grade rodenticide being weighed under a makeshift exhaust hood constructed from a bottomless barrel and suspended below an open propeller-type fan. The turbulence created by this system served only to disperse the contaminant and increase personnel exposure. The employees who had constructed this so-called exhaust system were unaware that it could not work. In another incident, a technician operated a homemade trichloroethylene degreaser constructed from a kitchen sink. The draining board was equipped with a series of infrared lamps which dried suspended metallic parts and evaporated the solvent from the open-sink well. A lengthy discussion with this technician as to the precautions to be used and the modifications required to make this system functional convinced him of the need to procure a commercial degreaser. Frequently, such a person is amazed to learn that many of the safeguards he needs are available commercially.

A third category of research installation personnel are not directly associated with research as such but are exposed to its hazards. These include maintenance and janitorial workmen. Tearing down a laboratory hood or repairing a ventilating system can result in serious chemical burns and systemic poisoning. A mercury-contaminated mop can expose secretarial and other office personnel to contamination. Recently, during a tour of a facility, one of our industrial hygienists noticed an unlocked door at the end of a dimly lit corridor. The door was posted with two signs—CAUTION. RADIOACTIVE MATERIALS. WATCH YOUR STEP. The door opened to a room below grade, accessible only by a vertical ladder. The doorway could cause a serious fall, and the situation was quickly corrected.

Benefits From Evaluation

Many research installations have highly skilled safety representatives. Too frequently, however, these persons are employed in only an advisory capacity. Many do not have the authority to enforce safety practices, nor are they informed of new projects and layout changes. Periodic inspections of research facilities by trained industrial hygienists tend to strengthen the safety engineer's position in his organization. Safety representatives welcome assistance and helpful suggestions from the industrial hygienist. A visit from a trained observer is most vital to the smaller laboratories which do not have, and probably could not afford, the services of persons versed in health protection and safety.

In providing service to the research installation, the governmental occupational health program benefits by being able to tool up for future hazards in industry. Some of the solvent formulations and new chemical linkages in plastics that we have previously seen in research laboratories are now coming into use in industrial plants. In addition, some of the laser-generating devices observed on the laboratory bench when the evaluation project was first begun are now used in industry. Many examples could be cited to show the advantages of inspecting research installations routinely and offering them service.

When the evaluation project was being considered in 1964, many problems had to be examined and resolved. Research installation personnel are generally unfamiliar with the inspection procedures applied to industry. They are engaged in proprietary activities, and it was feared that they might resent outside interference. They operate on tight time-schedules which cannot be interrupted. Such persons, it was believed, might resist and refuse advice from the outside altogether.

Despite some apprehension, the evaluation project was, however, initiated. Contrary to expectations, the service offered was gratefully accepted. In one instance early in the project, a research director requested that we make a complete tour of his facility, not being aware that an inspection was the intent of our visit. Most research personnel are eager to discuss their activities. They freely discuss means of minimizing their exposure to contaminants and listen avidly to any suggestions given. They are willing to discuss errors and correct unhealthful situations. Most of all, research personnel appreciate learning whom they may call for consultation and assistance.

The cost of occupational disease represents a significant expense to the employee, the employer, and the general public. In research, many famous scientists have suffered from exposure to the products they have developed. It is not known, nor can it be estimated, how many research workers have been affected by the materials and machines they have developed. Yet both from the humanitarian and the economic standpoint, research installations should be models of healthful working environments. Industrial hygienists have an important and essential role in protecting the health and well-being of the researcher.

EDITOR'S SECTION

PEDIATRIC RESIDENCIES AND FELLOWSHIPS

In addition to the regular input of pediatric residents into the inservice programs, a limited number of Pediatric Fellowships will be available to fully trained Pediatricians to commence in the summer of 1968 in selected civilian institutions. These fellowships are normally one year in duration. Applications should be submitted in accordance with BUMED INSTRUCTION 1520.10C in time to reach BUMED prior to 1 July 1967. Applicants are authorized to make tentative arrangements with accredited civilian institutions of their choice, but it must be made clear to the institution that final acceptance is dependant upon applicant's selection by the Bureau's Professional Advisory Board.

Also, in addition to the regular input of first year Pediatric residents, a limited number of third year inservice billets will be available to present first year Pediatric residents to begin in the summer of 1968. Any first year Pediatric resident wishing to continue through the third year should request same through channels prior to 1 July 1967.—Training Branch, BuMed.

MK-6 LIFE PRESERVER

The cause of a recent A-1 aircraft pilot drowning at sea has been traced to the increased weight of personal survival equipment now being carried by pilots in combat areas. In response to the urgent need of A-1 pilots for increased life preserver buoyancy to support the weight of increased personal survival equipment, the Aerospace Crew Equipment Laboratory has developed a new inflatable life preserver designated the MK-6. The new MK-6 preserver has 65 pounds of buoyancy and is designed as an across-the-board replacement for the present use of the MK-2 life vest, which has only 20 pounds of buoyancy, and the MK-3 life vest which has 55 pounds of buoyancy. The MK-6 will come in two types: Type I for use on propeller aircraft, and Type II for use on fighter/attack jet aircraft.—Public Affairs Office, BuMed.

17-YEAR STRUGGLE ENDS—NAVY HOSPITAL OPENS

A 17-year struggle to establish a modern medical facility for the needs of area Navymen ended at 2 p.m. Wednesday, February 1, with the commissioning of the Long Beach Naval Hospital.

Two local dignitaries who were instrumental in paving the way for final approval of funds for the hospital, Congressman Craig Hosmer (R-Cal.) and Long Beach Mayor Ed Wade, joined with Navy officials at the dedication ceremony.

Congressman Hosmer made the principal address. Other dignitaries on the platform were the Navy's Surgeon General, VADM Robert B. Brown; RADM Frank A. Brandley, Commandant of the 11th Naval District; RADM Carlton B. Jones, Commander of the Naval Base Los Angeles; and RADM Horace D. Warden, 11th Naval District Medical Officer.

CAPT Paul R. Engle, a Navy doctor, commands the hospital. His last duty station was aboard the hospital ship USS REPOSE where he served as commanding officer of the hospital in that ship. Part of his tenure on the ship was spent in Vietnamese waters.

The $7.5 million structure replaces the old hospital ship HAVEN which is currently berthed at the Long Beach Naval Station on Terminal Island. The HAVEN has provided the only extensive hospital care for thousands of Navymen since the Navy's old hospital in Long Beach was turned over to the Veterans Administration in 1950, and another medical facility was disestablished in Corona in 1957.

The new hospital, authorized by Congress in 1962, has been under actual construction since January, 1965. Groundbreaking for the 60-acre site occurred on April 30, 1964. The land for the hospital, situated on Carson Street near the San Gabriel Freeway, is leased to the Navy by the City of Long Beach for a nominal $10 a year.

The hospital is a five-floor, reinforced concrete building of 210,500 square feet and is completely air conditioned. Facilities include a 350-bed inpatient capacity and outpatient clinics for medicine, surgery, dentistry, dermatology, eye, ear, nose and throat, gynecology, orthopedics, pediatrics, and psychiatry. In addition, adjunct clinical facilities are provided for radiology, laboratory, physical therapy and central surgical supply.

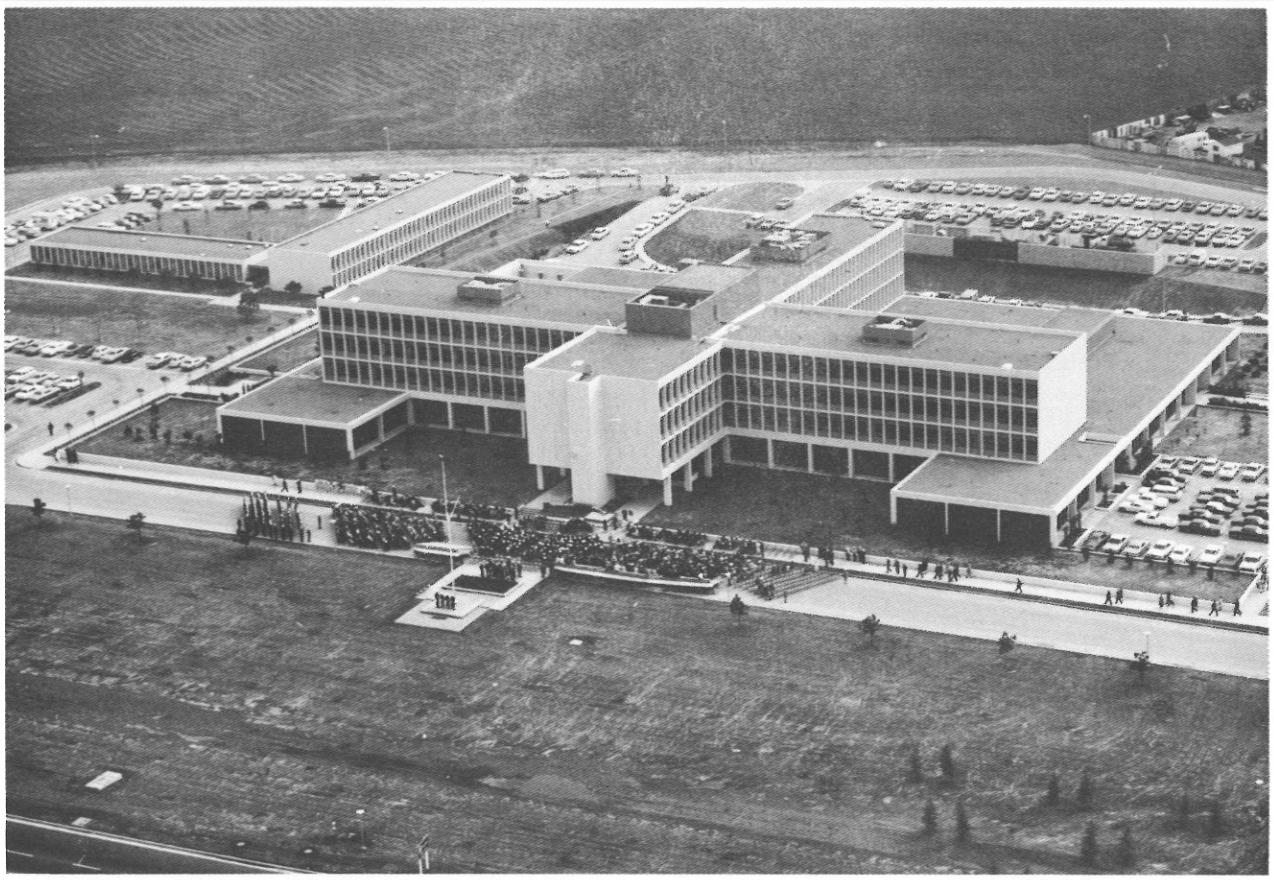
The main building also contains a modern cafeteria and recreation lounge, a Navy Exchange annex and a snack bar. Offices are provided for the Red Cross and the Grey Ladies.

One of the most impressive ancillary facilities is the 35-seat chapel with stained glass windows and chapella. Adjacent structures house rooms for 108 enlisted men and separate quarters for 34 Waves.

The hospital contains the latest communication equipment: pneumatic tubes system for speeding messages and diagnostic study requests and reports to various stations throughout the building; a central dictation system; TV in patients' rooms and recreation areas; FM music piped throughout the hospital; and pocket radios for paging staff personnel.

The plans for the hospital were prepared by the architectural firm of Hugh Gibbs and Donald Gibbs of Long Beach under contract to the Director, Southwest Division of Naval Facilities Engineering Command. The primary design recognizes the therapeutic value of pleasing architecture and attractive use of materials. Special attention has been given to efficient movement of air and the sound deadening of all vibrations generated by support equipment.

The ground floor contains the service departments and machinery spaces. The first floor houses the administrative offices, outpatient clinics, diagnostic services and surgical suite. The second to fourth



—Official U.S. Navy Photograph

floors contain the nursing units, including individual intensive care units for medical and surgical patients.

The Long Beach economy will be beefed up by the addition of $3.5 million annually as a result of the hospital's opening. Civilian employee wages and military pay will make up most of this total with $250,000 expected to be spent for supplies and services.—By Lee Quinn JOC USN, Public Affairs Office, Long Beach, Calif.

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